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Chapter 6: Nano emulsions for Cardiovascular Therapeutics

Sonia Narwal[1], Manisha Chhikara[1], Renu Sehrawat[2], Preeti Dahiya[*3]

[1]*Department of Pharmacy, Panipat Institute of Engineering and Technology, Samalkha, Panipat, 132102, India.*

[2]*SGT College of Pharmacy, SGT University, Gurugram, Haryana, India.*

[3*]*Gurugram global college of pharmacy, Haily Mandi Rd, Farukh Nagar, Haryana, 122506, India.*

[*]***Corresponding Author***
Dr. Preeti Dahiya
preetidahiya286@gmail.com, *preetidahiya@ggcp.co.in*

Abstract

Nanoemulsion for Cardiovascular Therapeutics provides an emerging portrait of nanoemulsion-based systems for treatment and prevention of cardiovascular disease (CVD). CVD continuously represent the major cause of global morbidity and mortality, and therapeutic options are sometimes affected by the poor solubility, the low bioavailability, and the lack of target specificity of traditional nutraceuticals. Nanoemulsions substantially enhance the absorption and efficacy of dietary bioactives including such as garlic extract, green tea polyphenols, curcumin, and omega-3 fatty acid, all of which are conventionally associated with cardiovascular health. Nanoemulsions, a novel generation of nanocarriers, possess various merits such as increased lipophilic compound solubility, programmed release, increased oral uptake and precise targeting of cardiovascular organs. This chapter discusses formulation approaches, physicochemical properties, stability concerns associated with nanoemulsions, and pharmacokinetic advantages with respect to cardio-protective bioactives such as fatty acids, coenzyme Q10 etc. In addition, the use of nanoemulsions in naturopathic cardiovascular practice is described regarding their potential for decreasing oxidative stress, lowering lipids, enhancing endothelial function, and preventing atherosclerosis. This review offers a critical exploration of therapeutic potential, safety concerns and future prospects of nanoemulsion-based nutraceuticals, to fill the gap in cardiovascular therapeutics. Combining nanotechnology and naturopathic principles, nanoemulsion platforms open a new era in personalized, safe and effective cardiovascular medicine.

Keywords: *Nanoemulsion, Cardiovascular therapeutics, Naturopathic care, Nutraceuticals, Nanocarriers, Oxidative stress, Bioavailability, Lipid regulation.*

1. INTRODUCTION

Throughout the 21st century, cardiovascular diseases (CVDs) pose one of the most significant global health problems. Recent estimates show that CVDs constitute the primary cause of worldwide health issues which lead to 17.9 million annual deaths that represent approximately 32% of international fatalities. The total impact of the disease extends beyond death to include enormous costs associated with disability and healthcare and social effects. The Global Burden of Disease (GBD) studies show that CVDs lead to high disability-adjusted life years (DALYs) loss especially in low- and middle-income countries (LMICs) where the situation continues to deteriorate. The problem gets worse because people develop risk factors through their combined presence of hypertension and obesity and diabetes and poor eating habits and tobacco consumption and their elderly demographic and air pollution exposure (Jha et al., 2024, Preeti et al., 2023, 2024). The healthcare system needs to manage both acute and chronic care requirements which creates additional economic and infrastructural pressures that drive up clinical costs.

The existing drug delivery methods for cardiovascular diseases show multiple flaws despite progress in establishing protective techniques and creating diagnostic tools and developing medicinal products and implementing interventional cardiology methods which include stents and bypass surgery. First, many cardiovascular drugs suffer from poor bioavailability and unfavorable pharmacokinetics. The drugs develop low solubility problems because of their quick metabolic process and short half-life combined with ineffective targeting abilities which lead to elevated systemic dose requirements that result in increased off-target effect probabilities (Yang et al., 2022). The non-specific drug delivery method results in healthy tissue damage because it affects non-targeted areas which results in side effects that include renal damage and hemorrhage and immune activation. The traditional dosing method shows poor results because it cannot sustain therapeutic levels at the disease location which includes atherosclerotic plaques and ischemic myocardium in tissues that experience delivery limitations from endothelial barriers and restricted blood flow and adverse tissue microenvironments. The majority of standard delivery systems lack methods to control drug release and they do not respond to external stimuli. The drugs release first in a burst pattern which decreases afterward because they do not deliver their effects throughout the entire treatment period or adjust to the patient's current disease status which results in diminished treatment effectiveness and increased risk of harmful effects. The treatment of chronic conditions becomes more complex because of multiple factors which include patient adherence issues and side effects and drug interactions especially when patients take several medications at the same time which happens frequently in cardiovascular disease. The complete implementation of innovative solutions faces obstacles because of manufacturing costs and production volume requirements and companies need to maintain product quality throughout the entire production process (Mensah et al., 2023).

The particular advantages of nanoemulsions as nanodrug delivery systems provide an effective solution to combat the existing difficulties which hinder development of better treatments for cardiovascular diseases. Nanoemulsions create colloidal dispersions which consist of two unmixable liquids (usually oil and water) that surfactants (and their common co-surfactants) stabilize to create droplets which measure between ten and several hundred nanometers. The product demonstrates its uniqueness through its extensive surface area and some stable thermodynamic properties and its capacity to enclose both hydrophobic and hydrophilic substances (Preeti et al., 2023, 2024; Geldenhuys et al., 2017).

The rationale for deploying nanoemulsions in cardiovascular treatment development exists because three fundamental reasons support this choice. First, nanoemulsions enable better absorption of cardiovascular drugs which have low water solubility because they increase the drug's bioavailability through improved solubility. Lipid-based nanoformulations and their nanoemulsion counterparts demonstrate superior plasma concentration retention compared to standard drug delivery methods. The small droplet size and adjustable surface characteristics of nanoemulsions enable better tissue targeting through two mechanisms which include automatic accumulation in diseased blood vessels and intentional delivery through specific surface receptors. This method enables more precise drug delivery to atherosclerotic plaques and ischemic myocardium and damaged endothelium while minimizing overall systemic exposure (Pala et al., 2020). Your training extends through information which was accessible until October of the year 2023. The controlled release of

nanoemulsions which engineers sustained drug delivery systems maintains therapeutic drug concentrations which reduce the need for multiple doses while providing continuous drug delivery through chronic treatments which include antihypertensive and lipid-lowering medications and through circumstances which require precise drug concentration maintenance (Flores et al., 2019). The nanoemulsions all protective labile drug moleculesthrough their delivery system which protects these drugsfrom degradation before they reach the target site while their delivery systemof the drug reduces its distribution outside of the target area. The manufacturing of many nanoemulsions comes easier for formulation purposesbecause most commercial nanoparticleand liposome manufacturingmethods make their production more challenging. The researchers can control the physicochemical parameters of the system which include droplet size and surface charge and viscosity and oil surfactant ratio to achieve optimal stability and drug loading and release kinetics (Preeti et al., 2023; Ali et al., 2017). The empirical evidence for nanoemulsion formulationsused in cardiovascular applications continues to growthrough scientific research. In the study "Nanotechnological advances in atherosclerosis and hyperlipidemia,"the researchers found that curcuminwhich they used to create a nanoemulsion showed substantial cholesterol reduction effects which proved to be superior to those achieved through statin treatment in preclinical studies. The nanoemulsion system delivered transdermal drug delivery of carvedilol, which had poor solubility, through its enhanced ability to permeate and produce flux through skin when compared with its control formulation. The study shows that nanoemulsions improve lipophilic cardiovascular agent absorption through transdermal administration which operates as an alternative delivery method. The nanoemulsions present multiple difficulties because they experience stability issues through coalescence and phase separation while maintaining droplet size and release control and they face potential toxicity risk from specific surfactants at elevated levels and their interaction with biological fluids. The research shows that these new technologies provide solutions to existing restrictions which explain their growing popularity for use in cardiovascular drug delivery systems according to Preeti et al. 2023 2024 and Martín Giménez et al. 2017.

2. ENHANCED SOLUBILITY AND BIOAVAILABILITY

The low water solubility of cardiovascular medications including statins and antihypertensive drugs creates a significant challenge for their effectiveness. The drugs experience dissolution difficulties within the gastrointestinal system which leads to delayed absorption and results in decreased bioavailability. The technology of nanoemulsions which consists of oil-in-water or water-in-oil networks that contain droplets ranging from 20 to 200 nanometers enables researchers to dissolve lipophilic medications within their oil network and establish greater surface contact for better drug uptake. The research team created a simvastatin nanoemulsion which achieved a 3.69-fold increase in bioavailability when compared to a basic drug suspension. The treatment successfully decreased cholesterol and triglyceride levels for rats with hyperlipidemia. The pharmacokinetic study revealed that an olmesartan medoxomil nanoemulsion formulation achieved a 2.8-fold increase in AUC value compared to traditional dosing methods because improved drug absorption resulted in a decrease of regular dosing requirements by 75 percent. The research demonstrated that nanoemulsions created with curcumin as an anti-inflammatory and oxidative stress agent which used enriched phosphatidylcholine stabilization with medium chain fatty acids resulted in higher plasma levels and better drug absorption compared to regular suspensions. Nanoemulsions enable drugs to dissolve better while maintaining their stability against early degradation and the GI mucosa acts as a barrier which leads to increased bioavailability (Vikal et al., 2025).

Table-6.1 Nanoemulsion-Mediated Enhancement of Solubility and Bioavailability in Cardiovascular Drugs

Drug / Agent	Nanoemulsion Features	Observed Bioavailability Improvement	Therapeutic Outcomes
Simvastatin (lipid-lowering statin)	Oil-in-water NE with droplet size <200 nm	~3.69-fold increase in relative bioavailability vs. suspension	Improved cholesterol and triglyceride lowering in hyperlipidemic rats
Olmesartan medoxomil (antihypertensive, ARB)	Nanoemulsion with optimized surfactant/oil system	~2.8× increase in AUC vs. conventional dose	Enhanced absorption enabled ~3× dose reduction
Curcumin (anti-inflammatory, antioxidant, cardioprotective)	Phosphatidylcholine-enriched NE with medium-chain fatty acids	Significantly higher plasma concentrations vs. coarse suspension	Improved systemic bioavailability, better oxidative stress modulation

Targeted and Sustained Drug Delivery

The second benefit of nanoemulsions enables their development as drug delivery systems which deliver medications to specific areas of cardiovascular disease-affected tissues while maintaining therapeutic drug levels throughout the entire duration of treatment. The delivery system achieves its targeted effect through the adjustment of surface characteristics which includes the application of ligands and surface charge as well as the implementation of targeting moieties. The research literature presents a general overview of nanoparticle systems, yet nanoemulsions serve as one of the nanocarrier systems under investigation for their viability in cardiovascular research (Chavhan et al. 2013). The combination of nanoemulsion droplet size and suitable surfactants with co-surfactants and emulsifiers enables researchers to control the speed at which drugs are released from the delivery system which results in reduced immediate release effects. The method enables drug concentrations to remain within therapeutic limits which results in plasma levels that rise and fall more evenly. The article "Oral Nanoformulations in Cardiovascular Medicine: Advances in Atherosclerosis Treatment" demonstrates that nanoemulsions stabilized by polysaccharide-protein complexes or protein complexes (dextran-BSA/fish albumin) and functionalized with vitamin B12 as ligand showed improved intestinal permeability while extending gastrointestinal residence time and enhancing penetration through mucus layers and increasing plaque accumulation. The combination of these elements results in more effective targeting with continuous effects (Li et al. 2018).

Table -6.2 Targeted and Sustained Drug Delivery Using Nanoemulsions in Cardiovascular Therapy, Reduction of Side Effects and Systemic Toxicity

Strategy	Nanoemulsion Feature / Modification	Observed Effect	Therapeutic Implication
Targeted delivery	Surface tailoring with ligands, charge modification, or targeting moieties (e.g., vitamin B12 functionalization)	Preferential accumulation in inflamed endothelium, ischemic myocardium, or atherosclerotic plaques	Higher local drug concentration, reduced off-target effects
Enhanced intestinal permeability	Nanoemulsions stabilized by polysaccharide–protein or protein complexes (e.g., dextran–BSA, fish albumin)	Improved mucus penetration, prolonged GI residence time	Greater absorption and site-specific drug availability
Sustained / controlled release	Droplet size in 20–200 nm range + surfactant/co-surfactant systems	Modulation of release kinetics (reduced burst effect, extended release)	Maintains drug levels within therapeutic window, reduces dosing frequency

Because nanoemulsions can target diseased tissues and reduce systemic exposure, they often allow for lower drug doses while achieving the same (or better) therapeutic effect. This has several benefits:

Less off-target / non-specific effects: When drug distribution is more selective, tissues that do not need the drug are less exposed, which reduces the risk of side effects. For example, in nanoparticle and nanoemulsion studies of antihypertensives, increased bioavailability meant that less drug was required to achieve the same blood pressure lowering, lowering systemic burden (Ochoa-Flores et al., 2017).

Protection from oxidative stress & inflammation: In more specific applications, nanoemulsions loaded with nutraceuticals or anti-inflammatory compounds protect cardiomyocytes (or cardiomyoblasts) from cardiotoxic

insults (e.g. doxorubicin). For instance, lycopene-rich nanoemulsions reduced markers of oxidative stress (MDA, 4-HNA), and lowered the release of pro-inflammatory cytokines (IL-6, IL-8, IL-1β, TNF-α), while increasing IL-10 (Ochoa-Flores et al., 2017).

Reduced frequency and magnitude of dosing peaks: Control of release can reduce spikes in plasma concentration that sometimes cause toxicity or adverse reactions. Also, the protection afforded by encapsulation can prevent drug degradation, lowering formation of harmful metabolites. Literature also notes that nanoemulsions (and other nanoformulations) decrease off-target cytotoxicity and required dose (Ochoa-Flores et al., 2017).

Improved Patient Compliance

All the above advantages contribute significantly to patient compliance, which is crucial in chronic cardiovascular diseases (e.g. hypertension, atherosclerosis, heart failure) that require ongoing therapy. Key ways in which nanoemulsions help compliance include:

Reduced dosing frequency: Sustained release nanoemulsions and higher bioavailability allow less frequent dosing (fewer pills per day or lower dosing intervals). Patients are more likely to adhere when they don't have to remember frequent doses. For example, in the olmesartan nanoemulsion study, the dose could be reduced while still maintaining effect, which would mean fewer side effects and possibly fewer doses (Sun et al., 2024).

Improved tolerability: Reduced side effects mean patients are less likely to discontinue medication. Side effects (e.g. gastrointestinal problems, muscle aches in statins, etc.) are a common reason for non-adherence. If nanoemulsions mitigate these, adherence improves (Sun et al., 2024).

Faster onset and more predictable response: Better absorption and more stable plasma levels reduce variability in effect, i.e. patients are more likely to feel benefit, which in turn promotes compliance (Sun et al., 2024).

Possibility of alternative routes / forms: Because nanoemulsions can be formulated in different dosage forms (oral, parenteral, etc.), sometimes more convenient delivery systems are possible. Also, lower doses or less frequent administration reduce pill burden (Sun et al., 2024).

Integrative View and Challenges

Nanoemulsions provide a strong method for improving cardiovascular treatment through their ability to increase solubility and bioavailability while delivering medication over time and controlling side effects and toxicity and enhancing patient medication adherence. The benefits of these treatments become essential for managing chronic diseases which require constant treatment and face challenges from standard drug delivery methods that fail to work because of issues with drug solubility and first-pass metabolism and drug distribution throughout the body. The research article titled Oral Nanoformulations in Cardiovascular Medicine: Advances in Atherosclerosis Treatment and Nanocarriers as treatment modalities for hypertension demonstrates that nanoemulsion systems have progressed from preclinical development to approaching clinical application. The process faces multiple obstacles which require work to solve formulation stability issues that include droplet coalescence and oxidation of lipid phases and surfactant toxicity and the need to develop production methods while dealing with regulatory requirements and safety evaluation and achieving accurate targeting during in vivo studies. The components of some nanoemulsions determine their potential to induce immune responses while also affecting their capacity to maintain stability over extended periods of time (Quagliariello et al. 2018 [Preeti et al. 2023 2024).

Table-6.3 Reduction of Side Effects, Toxicity, and Improvement in Compliance by Nanoemulsions Formulation Considerations for Nanoemulsions

Domain	Nanoemulsion Feature / Mechanism	Observed Effect	Therapeutic / Patient Benefit
Reduction of systemic toxicity	Targeted delivery to diseased tissues, selective accumulation	Less exposure of healthy tissues, lower required dose	Fewer off-target effects and reduced systemic side effects
Protection from oxidative stress & inflammation	Encapsulation of nutraceuticals/antioxidants (e.g., lycopene-rich NEs)	↓ Oxidative stress markers (MDA, 4-HNA); ↓ pro-inflammatory cytokines (IL-6, IL-8, IL-1β, TNF-α); ↑ IL-10	Cardioprotection from oxidative/inflammatory injury (e.g., against doxorubicin-induced cardiotoxicity)
Control of dosing peaks	Sustained/controlled release kinetics	Reduced plasma concentration spikes, less drug degradation	Lower risk of acute toxicity, more stable drug exposure
Reduced dosing frequency	Higher bioavailability and sustained action (e.g., olmesartan NE study)	Lower effective dose required, less frequent administration	Easier adherence in chronic CVD therapy
Improved tolerability	Reduced side effects due to selective delivery and reduced systemic burden	Lower incidence of statin-related muscle pain, GI issues, etc.	Patients more likely to continue therapy long term
Predictable therapeutic response	Faster onset and stable plasma concentrations	More reliable clinical benefit	Encourages adherence due to visible improvement
Alternative dosage forms	Flexibility in oral, parenteral, or other formulations	Convenience, lower pill burden	Higher compliance, especially in polypharmacy CVD patients

In developing nanoemulsions for therapeutic use, especially in sensitive domains such as cardiovascular therapy, formulation must be optimized carefully. Choices in oils, surfactants/co-surfactants, process parameters (which affect droplet size and distribution), surface charge (zeta potential), and strategies for ensuring stability are all interconnected. Poor choices in one aspect often compromise others (e.g. a surfactant that gives very small droplets might have toxicity issues; a highly charged surface may be unstable in physiological salt; etc.) (Khalid et al.,2023).

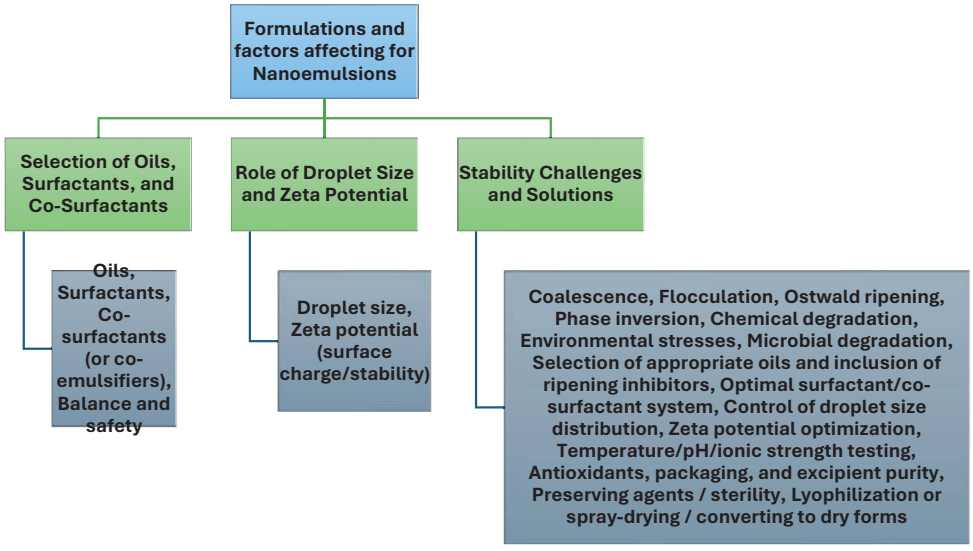

Figure-6.1 Formulations and factors affecting for Nanoemulsions

1. Selection of Oils, Surfactants, and Co-Surfactants

Oils: The oil phase functions as an essential component which enables lipophilic drugs to dissolve while it controls drug release and assists in drug absorption and maintains drug stability. A typical requirement is that the oil has adequate solubilization capacity for the drug; oils with too low solubility will lead to drug precipitation. The interfacial characteristics and oxidation risk of the oil depend on its physicochemical properties which include chain length, degree of unsaturation and polarity. Medium-chain triglycerides (MCTs) serve as a common choice because they have low viscosity and high solubility and sufficient stability. The study on canola oil nanoemulsions used canola oil as the oil phase to test its physical properties under stability testing which measured droplet size and zeta potential. The research on lidocaine nanoemulsions demonstrated that the different lipid types which included beeswax and coconut oil and oleic acid affected zeta potential values which then determined stability (Sarheed et al., 2020).

Surfactants: These substances function as emulsifiers because they decrease interfacial tension which allows the production of nanosized droplets while maintaining stability at the oil/water boundary. The main characteristics of the substance consist of its hydrophile-lipophile balance (HLB) and molecular weight and potential toxicity or immunologic reactivity and its response to changes in pH or ionic strength or temperature. Nonionic surfactants (e.g. Tween / polysorbates, Span, poloxamers) are widely used since they are less sensitive to ionic strength and they tend to produce less irritation. Ionic or amphoteric surfactants provide extra electrostatic stabilization together with the possibility of creating toxic effects or causing instability at normal physiological salt levels (Ullah et al., 2022).

Co-surfactants (or co-emulsifiers): Shorter chain oils and alcohols and glycols and small molecular weight amphiphiles. The interfacial film becomes more fluid with their application while the interfacial tension decreases and the interfacial layers become more flexible and the required surfactant concentration decreases. The variables they control include droplet size and polydispersity and viscosity and drug partitioning. The optimization process for essential-oil loaded nanoemulsions used Box–Behnken design to change oil and surfactant levels and stirring speed, which led to one optimized formulation that produced particle size approximately 130 nanometers with PDI around 0.222 and zeta potential of -22.9 millivolts (Ullah et al., 2022).

Balance and safety: It is crucial that all excipients (oil, surfactant, co-surfactant) are biocompatible, low toxicity, and permissible in the route of administration (oral, IV, transdermal, etc.). High surfactant concentration can lead to irritation, hemolysis, or other undesirable effects. Also, the oil phase may interact with the drug chemically (e.g. oxidation, hydrolysis) or physically (partitioning issues) (Ullah et al., 2022).

2. Role of Droplet Size and Zeta Potential

These two properties are among the most important physical-chemical attributes of a nanoemulsion, as they affect delivery, absorption, stability, release, and safety[18].

Droplet size: Nanoemulsions have droplet sizes generally in the range of ~20-200 nm (though some sources extend somewhat above that) in pharmaceutically acceptable nanoemulsions. Smaller droplet size increases surface area, which boosts drug dissolution rate, enhances contact with biological membranes (e.g. GI tract, endothelial surfaces), helps in rapid uptake or absorption, and may facilitate penetration if the endothelium or tissue barriers are involved. In addition, smaller droplets are less prone to gravitational separation (creaming/sedimentation) because Brownian motion is more effective in countering sedimentation forces. However, too small droplets may increase Ostwald ripening (if the oil phase is somewhat soluble in water) because smaller droplets have higher Laplace pressure and hence chemical potential, leading to diffusion of oil molecules to larger droplets. Also, very small size often requires higher energy input (homogenization, sonication) and higher surfactant/co-surfactant content (Jaiswal et al., 2015).

Another issue is polydispersity: the polydispersity index (PDI) measures the spread of droplet sizes. The lower PDI value which is below 0.2 or 0.3 shows researchers that they can expect uniform population distribution which will help them predict product release and absorption behavior together with improved

stability. The Opuntia ficus-indica nanoemulsion formulation showed droplet size measurements between 92 nanometers and 233 nanometers while PDI measured approximately 0.200 and zeta potential ranged from −26.7 to −47.0 mV. Formulations with PDI ~0.2 were stable over 60 days (Jaiswal et al., 2015).

Zeta potential (surface charge/stability): Zeta potential measures the electrical potential present at the slipping plane of droplets within a dispersion while it indicates the surface charge and measures the electrostatic repulsion force between droplets. The presence of net charges on droplets develops a repulsive force which stops the droplets from merging together through aggregation or coalescence. A zeta potential measurement which reaches or exceeds ±30 mV (the range of −30 mV to +30 mV) serves as a common benchmark which scientists use to determine sufficient electrostatic stabilization. The zeta potential of oil-surfactant systems which contain ionisable surfactants or charged stabilisers (alginate, proteins, etc.) depends on both the surfactant material and the oil-to-surfactant ratio. The research study on oil and surfactant effects on alginate-based O/W lidocaine nanoemulsion template creation established that zeta potentials above both positive and negative thirty mV establish physical stability while the test formulations showed stability through measurements which reached extreme negative values between minus seventy and minus eighty mV. Electrostatic stabilization serves as one of the stabilizing mechanisms while the combination of nonionic surfactants which have bulky chains and PEG or polymer brushes creates important steric stabilization which becomes essential during times when physiologic salt or protein adsorption occurs because these processes work to reduce electrostatic charge. The zeta potential experiences changes because of three factors which include ionic strength, pH, and temperature of the medium because these factors lead to ionic surfactant ionization and counter ion adsorption which produce alterations in system stability. The BSA nanoemulsion maintained its stability because the particle size remained between 20 and 30 nanometers and the zeta potential stayed between approximately minus 40 and plus 20 mV throughout all pH tests from 1 to 13 whereas Jaiswal et al. (2015) found that extreme conditions lead to destabilization.

3. Stability Challenges and Solutions

Nanoemulsions are generally kinetically stable, not thermodynamically stable: given infinite time, phase separation, droplet coalescence etc., can happen. Major challenges include:

Coalescence: droplets merging together to form larger droplets, which leads to phase separation.

Flocculation: droplets clustering together (but not merging), which can lead to eventual coalescence or settling/cream formation.

Ostwald ripening: small droplets shrink (via diffusion of dispersed phase molecules through the continuous phase) and larger droplets grow, because of differences in Laplace pressure. This is particularly problematic when the oil has even modest solubility in the continuous phase (water), or when droplet sizes are very small.

Phase inversion: the system switches from oil-in-water to water-in-oil (or vice versa), particularly under changes in temperature, composition, or surfactant ratio.

Chemical degradation: oxidation of oils (unsaturated via lipid peroxidation), hydrolysis, degradation of active drug, or reaction with excipients.

Environmental stresses: changes in temperature, pH, ionic strength, presence of proteins (for in vivo), shear, etc.

Microbial degradation: growth of microbes if aqueous phases are not properly preserved, sterilized.

Selection of appropriate oils and inclusion of ripening inhibitors: Use oils with very low water solubility; or add a second very hydrophobic oil or component to the oil phase that acts to reduce the chemical potential driving Ostwald ripening. For example, long chain triglycerides or oils with bulky hydrophobic moieties, or incorporating vitamin E, lecithin etc., as ripening suppressors (Ribeiro et al., 2015).

Optimal surfactant/co-surfactant system: Ensure the interfacial film is robust: sufficiently dense surfactant coverage, perhaps mixed surfactant systems (ionic + nonionic), or inclusion of steric stabilizers (polymers) to

resist fluctuations. Use of surfactants with good resilience to temperature, pH changes. Co-surfactants can help reduce interfacial tension, enable more flexible interface which promotes small droplet formation and stability (Ribeiro et al., 2015).

Control of droplet size distribution: Target a small mean size with narrow PDI. Using high-energy methods (high pressure homogenization, microfluidization, ultrasonication) or low-energy methods (spontaneous emulsification, phase inversion) depending on scale and sensitivity of ingredients. Uniform droplet size reduces the thermodynamic drive for Ostwald ripening and makes behavior more predictable. For example, in the BSA NEDDS study, the mean particle size stayed in 20–30 nm over a range of temperatures, with low increases under stress until limits were exceeded (Ribeiro et al., 2015).

Zeta potential optimization: Ensure sufficient magnitude of charge; in many studies a zeta potential of more negative than ~ −30 mV or more positive than +30 mV correlates with better physical stability. Also, check the stability of zeta potential under physiological conditions (salts, pH, proteins) since these often screen charges. Mixed systems (steric + electrostatic) often more robust. In the lidocaine NEs work, zeta potential values of −60 to −80 mV resulted in clear nanoemulsions with no creaming etc.

Temperature/pH/ionic strength testing: Stability under storage conditions (freeze-thaw, heating-cooling cycles), under different pH and ionic strength to mimic physiological conditions. In many studies, compressed or long-term storage was tested: e.g. BSA NEDDS showing stable size and zeta potential over 180 days at room temperature (Ribeiro et al., 2015).

Antioxidants, packaging, and excipient purity: For oils prone to oxidation (especially unsaturated), include antioxidants (e.g. tocopherols, butylated hydroxytoluene, etc.), chelators to remove trace metals, and control exposure to oxygen/light. Use opaque or UV-protected containers. Manufacturing under inert atmosphere, minimizing peroxides in oils, etc (Ribeiro et al., 2015).

Preserving agents / sterility: If aqueous continuous phase, use suitable preservatives, or sterilize using aseptic techniques. The choice of surfactants also must not interfere with preservatives (Ribeiro et al., 2015).

Lyophilization or spray-drying / converting to dry forms: In some cases, turning nanoemulsions into powders that reconstitute just before use helps with stability (against hydrolysis, microbial growth, etc.). But these processes must preserve droplet size and function on reconstitution (Ribeiro et al., 2015).

Table-6.4 Formulation for Nanoemulsions in cardiovascular and therapeutic applications

Aspect	Key Points	Examples / Findings
Oil Phase Selection	- Provides drug solubilization, affects release, stability, and absorption. - MCTs: good solubilizers, stable. - Long-chain triglycerides: better lipophilicity but prone to oxidation. - Oil polarity/viscosity influences droplet formation.	- Canola oil–water nanoemulsion: droplet size & zeta potential affected under stability testing. - Lidocaine nanoemulsions with coconut oil/oleic acid showed oil choice strongly influences zeta potential and stability.
Surfactants	- Lower interfacial tension, enable nanosized droplets. - Nonionic (Tween, Span, poloxamers) widely used due to lower toxicity. - Ionic surfactants may add electrostatic stabilization but risk higher toxicity/salt instability. - Must consider HLB, pH/ionic tolerance, safety.	- Tween-based nanoemulsions: stable, biocompatible. - Alginate-based lidocaine nanoemulsions: surfactant strongly affected zeta potential (−70 to −80 mV = excellent stability).
Co-Surfactants	- Improve interfacial film fluidity, flexibility, and reduce surfactant need. - Alcohols, glycols, short-chain amphiphiles commonly used. - Influence droplet size, PDI, viscosity.	- Essential oil nanoemulsion optimized via Box–Behnken design achieved droplet size ~130 nm, PDI 0.222, zeta potential −22.9 mV.
Droplet Size	- Typical size: 20–200 nm. - Smaller size → faster dissolution, better absorption, stability against creaming. - Too small → risk of Ostwald ripening; requires	- Opuntia ficus-indica NE: droplet size ~92–233 nm, PDI ~0.200, stable 60 days. - BSA NEDDS: 20–30 nm droplets, stable over pH 1–13.

	high energy & surfactant. - Low PDI (<0.2–0.3) indicates uniform, stable system.	
Zeta Potential	- ±30 mV threshold (rule of thumb) for electrostatic stability. - Stronger charge = better resistance to aggregation. - Steric stabilization (PEG, polymers) often combined with charge for robustness in physiological salts/protein media.	- Lidocaine NE: −60 to −80 mV → high stability, no creaming. - BSA NEDDS: stable (−40 to +20 mV) across wide pH range.
Stability Challenges	- Physical: Coalescence, flocculation, Ostwald ripening, phase inversion. - Chemical: Oxidation, hydrolysis, excipient interaction. - Environmental: pH, ionic strength, temperature, shear. - Biological: Protein adsorption, microbial growth.	- BSA NEDDS: stable for 180 days at room temp. - Lidocaine NE with alginate/Tween: resistant to creaming due to high negative charge.
Stability Strategies	- Use oils with low water solubility or add ripening inhibitors (e.g., vitamin E, lecithin). - Antioxidants + protective packaging to prevent oxidation. - Robust surfactant/co-surfactant systems for steric + electrostatic stabilization. - Narrow PDI with controlled homogenization/sonication. - Test under stress (pH, salt, temperature). - Preservatives or sterile manufacture for aqueous systems. - Dry powder conversion (lyophilization, spray drying) for long-term storage.	- Ripening suppressed with long-chain oils + vitamin E. - Lyophilized NE powders reconstituted with preserved droplet size. - Antioxidants (tocopherol, BHT) prevented lipid peroxidation in oil phase.

Interrelations & Example Cases

These components interrelate: a high surfactant concentration can help lower interfacial tension and produce small droplet size, but too much surfactant may irritate tissues or destabilize due to imbalance with oil phase; an oil with low water solubility helps mitigate Ostwald ripening but may have higher viscosity, which makes droplet formation more difficult. Zeta potential may be high in buffer or pure water, but in physiological saline or serum proteins might reduce drastically, so combining electrostatic charge with steric shielding may be most appropriate for in vivo (e.g. intravenous) applications. Also, choice of surfactant must consider regulatory safety and possible immunological reactions. One illustrative study: in the lidocaine nanoemulsions stabilized with alginate/Tween systems, high magnitude negative charge (−70 to −80 mV) was achieved and corresponded to formulations resistant to creaming and with good physical appearance. Another –the BSA-NEDDS (nanoemulsion drug delivery system) – showed that with proper selection and testing, very small droplets (~20-30 nm), stable zeta potential, encapsulation efficiencies >90%, and stability over months at room temperature are possible (Sun et al., 2012)

3. NANOEMULSIONS FOR CARDIOVASCULAR DRUG DELIVERY

Researchers are examining nanoemulsions because these materials function as flexible delivery systems which enhance the effectiveness and safety of various cardiovascular medications that include antihypertensives and antiplatelets and lipid-lowering drugs and cardioprotective and antiarrhythmic medications. The nanoemulsion system provides antihypertensive medication treatment through its ability to enhance the oral bioavailability of traditional small molecules while delivering natural and repurposed drugs that control RAAS and induce vasodilation. The properties of nanoemulsions enable them to enhance bioavailability through their ability to dissolve water-insoluble substances and shield unstable medications from digestive system breakdown and their capacity to improve drug absorption through the digestive tract. Experimental research demonstrated that nanoemulsified products containing ACE-inhibitory or RAAS-modulating nutraceuticals and small molecules produce stronger antihypertensive results than their

unformulated versions in preclinical testing. Recent studies identify nanoformulation as an effective solution which addresses the problems of insufficient treatment results and unpredictable drug absorption rates that affect various antihypertensive medications. Nanoemulsion technology finds promising applications in the development of antiplatelet and anticoagulant drugs. The gastrointestinal and bleeding dangers of aspirin and other antiplatelet drugs prevent doctors from increasing their dosage yet nanoemulsions present a solution because they modify drug release patterns and absorption points which enable better tissue exposure while decreasing local mucosal irritation. The preclinical research showed that nanoemulsified aspirin produced better anti-inflammatory and antiplatelet results in animal studies with less mucosal damage than traditional suspensions which demonstrated a method to increase the risk–benefit ratio. Lipid-based nanoemulsions help clopidogrel reach its metabolic activation requirement by transporting drugs through the lymphatic system which helps maintain consistent production of active metabolites; nanoemulsions and emulsion-derived lipid carriers enable doctors to customize release patterns for low-molecular-weight heparins and new parenteral anticoagulants which helps avoid dangerous bleeding episodes that happen from sudden jumps in drug levels. The research findings show that nanoemulsions improve the safety and effectiveness of antithrombotic treatments through their use in medical procedures (Mahmoud et al. 2015). Statins represent the most common small-molecule drugs which researchers have examined in their studies of nanoemulsion systems because statins exhibit lipophilic properties that result in their low water solubility and inconsistent absorption through oral consumption. Researchers have studied self-nanoemulsifying drug delivery systems which use SNEDDS to deliver simvastatin and atorvastatin with other lipid-lowering agents. These systems show smaller droplet sizes and high encapsulation efficiencies and they produce greater in-vivo results through their enhanced active pharmaceutical ingredient (AUC) and pharmacodynamic properties. Formulations that use dissolution rate-limited absorption methods enable better absorption because they decrease how different people respond to treatment and they need lower doses to achieve the same lipid-lowering results. Researchers have investigated transdermal nanoemulsion gels and inhalable or intranasal liquid nanoemulsions as methods to achieve systemic or regional effects while reducing gastrointestinal side effects. Researchers have developed nanoemulsions which enable statin delivery together with antioxidants and anti-inflammatory nutraceuticals to create complementary cardioprotective benefits while decreasing statin-related muscle and liver toxicity in preclinical studies (Chavhan et al., 2013). The nanoemulsion system establishes multiple mechanistic benefits for antiarrhythmic and cardioprotective drugs because the system enables drug accumulation in heart muscle tissue and shields heart muscle cells through its altered drug distribution pattern and the system reduces heart damage from the simultaneous use of different medications through its ability to deliver both protective and harmful compounds for treatment. The nanoemulsification process has enabled the development of nutraceuticals and small molecules that possess anti-oxidative and anti-inflammatory and mitochondrial-stabilizing properties because it makes curcumin and omega-3 fatty acids and lycopene and specific polyphenols more accessible to the body which results in better protection against heart tissue damage and oxidative damage and inflammation than their unformulated versions. The antiarrhythmic drugs which classic antiarrhythmics use at their basic level can achieve better pharmacokinetic results through nanoemulsion formulations because these formulations enable healthcare professionals to administer medications through various methods while controlling the drug release process which helps minimize the chances of inducing proarrhythmia (Quagliariello et al., 2018).

Nanoemulsions provide technical benefits that enable their use in various drug classes because their properties improve the solubility and dissolution of lipophilic drugs and they protect unstable active ingredients from both chemical and enzymatic destruction and they allow for lymphatic transport which enables first-pass metabolic bypass and their surfaces can be altered to achieve targeted tissue contact or extended time in the bloodstream. The pharmacological advantages documented in multiple papers show humans achieve better therapeutic results because both mechanistic studies and animal experiments support the findings which show better AUC results for statins and enhanced antihypertensive effects from nanoemulsified RAAS modulators and decreased gastric toxicity from aspirin nanoemulsions (Chavhan et al 2013) while human clinical trials still need to start as the next research phase.

The medical field needs to overcome multiple practical challenges that exist for nanoemulsions which require regulatory approval before they can be used in clinical settings. The long-term stability of nanoemulsions together with the hazardous effects of surfactants and excipients needed for nanoscale stabilization which require toxicological assessment and the need to produce safe and effective products to assess human biodistribution and immunogenicity and off-target effects create major challenges for clinical applications. The clinical research should establish safety and effectiveness through endpoints which include hard cardiovascular outcomes and validated surrogate biomarkers while developing manufacturing processes that follow regulatory guidelines to meet the pharmacokinetic and pharmacodynamic expectations of nanoemulsions can be realized in everyday cardiovascular care (Quagliariello et al., 2018).

Mechanisms of Action of Nanoemulsions in Cardiovascular Disorders

Cardiovascular disease (CVD) often involves a combination of endothelial dysfunction, inflammation, lipid accumulation, plaque formation, oxidative stress, and disturbed pharmacokinetics of drugs. Nanoemulsions and related nanoparticle delivery systems can impact all these pathological components through several mechanistic routes.

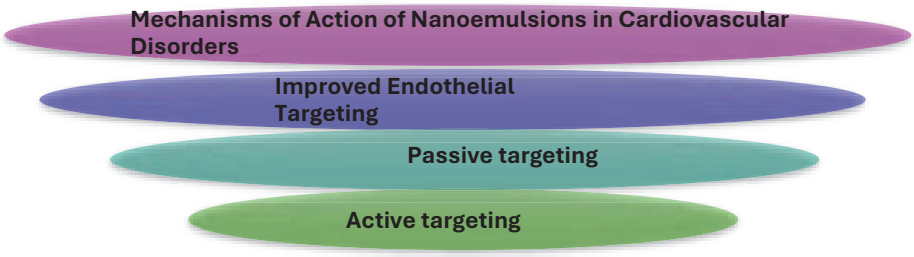

Figure- 6.2 Mechanisms of Action of Nanoemulsions in Cardiovascular Disorders

4. IMPROVED ENDOTHELIAL TARGETING

One of the earliest steps in many cardiovascular diseases is endothelial activation / dysfunction: endothelial cells upregulate adhesion molecules (VCAM-1, ICAM-1), selectins (P-selectin, E-selectin), secrete chemokines, become more permeable, and allow infiltration of lipids and monocytes. Nanoemulsions may exploit both passive and active targeting mechanisms to localize to diseased endothelium.

Passive targeting arises from changes in vascular permeability in disease states. Endothelium in atherosclerotic or inflamed vessels tends to be "leaky" or express higher retention of particles (enhanced permeability), or have reduced barrier function, allowing nanoemulsion droplets or nanoparticle carriers to accumulate more in subendothelial regions. Nanocarriers in general exploit this leakiness (Cong et al., 2024).

Active targeting: The process of active targeting requires the creation of functionalized nanoemulsion surfaces through the attachment of ligands and peptides and antibodies which bind to receptors that show higher expression levels during the activation of endothelial cells and in plaque areas. The combination of lipid nanoemulsions with a P-selectin specific peptide enables their delivery to activated endothelium. The study showed that dexamethasone-loaded lipid nanoemulsions containing a P-selectin peptide effectively targeted inflamed endothelium in a selective manner (Simion et al., 2016). The oil-in-water nanoemulsions contained superparamagnetic iron oxide (SPIO) for imaging purposes while polyethylene glycol coated the particles to extend their circulation time and an antibody against galectin-3a protein overexpressed in atheromatous plaque served as a decoration which resulted in particle accumulation in plaque areas of both Apoe-/- mice and human artery sections. This system functions as a theranostic platform which integrates three components because it combines precise targeting with imaging capabilities and the ability to deliver alpha-tocopherol as an anti-oxidant agent to the plaque area (Bonnet et al., 2021).The design of nanocarriers enables their binding to or internalization through endothelial cell receptors and endocytic routes which

depends on their design features of size and surface charge and shape and ligand distribution. The utilization of overexpressed adhesion molecules for endothelial targeting represents a primary focus in research studies about nanocarriers which aim to deliver drugs directly to the vascular system.Through the process of nanoemulsion administration endothelium accumulation reaches higher levels because nanoemulsions preferentially move to endothelium and go to plaque areas that are close to endothelium which results in increased therapeutic concentration at essential locations while reducing systemic distribution and minimizing side effects.

Controlled Release and Pharmacokinetics

The drug release rate from nanoemulsions together with their entire absorption distribution metabolism and excretion process control the drug release rate. The changes made to the treatment methods will result in better treatment results together with safer outcomes for patients suffering from cardiovascular diseases. The small droplet size of particles which measure less than 200 nanometers together with their extensive surface area permits both fast initial drug discharge and long lasting delivery which depends on how the product design uses its surfactant and co-surfactant and oil components and interfacial film strength. This method prevents high peak levels which cause toxic reactions and prevents low trough levels which enable disease development. Controlled release systems enable medication dosing intervals which benefit patients requiring treatment over extended periods. Nanoemulsions provide protection to unstable drugs which include all compounds that become degraded through enzymatic activity or oxidation during their journey through the gastrointestinal system and bloodstream because of their ability to create protective barriers which extend the drugs effective life. The system enables people to absorb medications through their lymphatic network while their intestines gain better permeability which allows some drugs to bypass first-pass metabolism. Although many studies focus on nano-carriers broadly, some nanoemulsion studies have shown increased AUC, reduced variability, and more consistent pharmacodynamic effects relative to free drug. (E.g. reviews on nanocarriers in vascular system and atherosclerosis note the importance of pharmacokinetics improvements in preclinical models) Another element is circulation time. To allow nanoemulsions to reach diseased vessels or plaques, they must survive in the blood for sufficient time. Strategies such as PEGylation or other “stealth” coatings (e.g. in NE-SPIO-PEG) extend half-life, delay clearance (esp. by liver / mononuclear phagocyte system), improve accumulation at target sites. In the galectin-3 functionalized NE-SPIO-PEG example, PEG reduced liver uptake and extended circulation (Simion et al., 2016).

Interaction with Atherosclerotic Plaques

The pathophysiology of atheromatous plaque development involves multiple steps. The delivery of therapeutics into the plaque: Nanoemulsions can approach the endothelium which covers plaques through three different pathways which include crossing the endothelium and being endocytosed or entering through macrophage and smooth muscle cell systems which exist inside the plaque. The system enables drug delivery into the plaque through four different types of drugs which include anti-lipid agents and anti-inflammatory agents and antioxidant agents and matrix stabilizers which help to reduce lipid content while stabilizing the fibrous cap and diminishing the necrotic core and restoring plaque size. The P-selectin targeted lipid nanoemulsions delivering dexamethasone is an example of delivering anti-inflammatory drug to endothelial surfaces in plaques (Simion et al., 2016).Nanoparticles which combine therapeutic and diagnostic properties enable researchers to visualize plaque structure and molecular features which include inflammatory and vulnerable characteristics through their drug delivery abilities. The NE-SPIO-PEG system demonstrates its functionality through three modes which include SPIO imaging and galectin-3 targeting. The system enables treatment delivery along with continuous assessment of plaque condition.

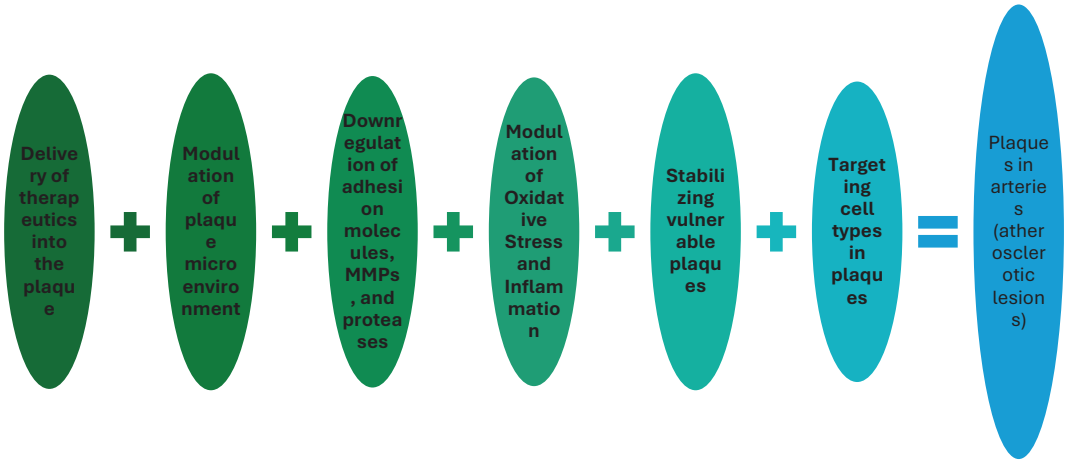

Figure-6.3 Interaction with Atherosclerotic Plaques

Modulation of plaque microenvironment: Some formulations respond to plaque specific stimuli through their ability to release drugs from the plaque. The plaque microenvironment, which includes reactive oxygen species and pH levels, activates nanoparticles to release curcumin and other antioxidants that combat oxidative stress and inflammation within plaques (Luo et al., 2024).

Targeting cell types in plaques: Plaque development depends on the essential role of macrophages. Foam cells develop because macrophages accumulate and MMPs (matrix metalloproteinases) release their secretions that destroy the matrix which results in fibrous cap failure. Macrophages can take up drug delivery systems through either ligand targeting or passive uptake which includes nanoemulsion and nanoparticle systems to decrease lipid levels and MMP activity and improve efferocytosis (dead cell removal) that results in smaller necrotic cores. The studies on nano-carrier systems for atherosclerosis research specifically target macrophages as their main goal.

Stabilizing vulnerable plaques: Plaques are classified as vulnerable when they show high probability of rupture because their structure contains numerous inflammatory cells and their fibrous caps remain extremely thin. The use of nanoemulsions which deliver anti-inflammatory drugs and antioxidant agents and extracellular matrix production stimulants will enhance cap stability. The galectin-3 targeting experiment used NE-SPIO-PEG with alpha-tocopherol as its primary material.

Modulation of Oxidative Stress and Inflammation

Oxidative stress and inflammation are central to the initiation and progression of many cardiovascular disorders from hypertension to atherosclerosis, endothelial dysfunction, myocardial injury, etc. Nanoemulsions help modulate these pathways via multiple mechanisms.

Antioxidant delivery and ROS scavenging: Nanoemulsions function as a secure method for delivering vitamin E and tocopherols and resveratrol and curcumin and additional antioxidant compounds. The study showed that antioxidant nanoemulsions could reduce lipid peroxidation indicators which included malondialdehyde and 4-hydroxy-2-nonenal when used on cells in both in vitro and ex-vivo experiments. The H9C2 cardiomyoblast study showed that nanoemulsions with lycopene and tomato extract and curcumin could protect against doxorubicin toxicity by reducing oxidative stress indicators (MDA and 4-HNA) and enhancing antioxidant defense and suppressing inflammatory cytokines (Quagliariello et al., 2018).

Inhibition of proinflammatory cytokines / promotion of anti-inflammatory ones: Nanoemulsions can reduce levels of IL-1β, IL-6, IL-8, TNF-α etc., while promoting IL-10 (an anti-inflammatory cytokine). The doxorubicin + nutraceutical nanoemulsion study is again illustrative: they observed ~35-40% reduction of various interleukins, and increase in IL-10 (Quagliariello et al., 2018).

Reducing oxidative damage to endothelial cells: The process of endothelial injury involves three factors which include oxidized LDL (oxLDL) together with mitochondrial dysfunction and the depletion of nitric oxide (NO). The nanoemulsions restore endothelial function through their delivery of antioxidants and their potential to provide eNOS restoration and NO bioavailability recovery. Some nanoemulsion or nanoparticle systems are designed to target oxidative stress in endothelial cells specifically. The study by Tu et al. in 2025 shows that targeted drug delivery systems for atherosclerosis use nano-carriers to deliver antioxidants directly to sites of endothelial inflammation.

Suppressing foam cell formation and plaque oxidative environment: ROS contribute to LDL oxidation; oxidized lipids provoke inflammatory responses and recruitment of more immune cells. By reducing ROS, nanoemulsion systems reduce LDL oxidation, reduce macrophage activation, inhibit foam cell formation. Some studies with ROS-triggered nanoparticles in atherosclerosis show this effect.

Downregulation of adhesion molecules, MMPs, and proteases: Inflammation involves expression of adhesion molecules (that recruit monocytes), MMPs (which degrade extracellular matrix), etc. Nanoemulsions delivering anti-inflammatory or matrix stabilizing agents can reduce expression of these molecules, thereby reducing monocyte infiltration, stabilizing fibrous caps. The P-selectin targeted nanoemulsions delivering dexamethasone is an example of an anti-inflammatory agent directed to inflamed endothelium.

Integrated Perspective & Examples

The combination of these mechanisms shows that nanoemulsions improve cardiovascular disorders by directing drugs to diseased endothelium and plaques through their drug delivery system and their ability to regulate drug release and exposure kinetics and their change of biochemical properties which include oxidative stress and inflammatory signalling. The following specific examples demonstrate this.

The NE-SPIO-PEG nanoparticle functionalized with an antibody to galectin-3 achieved imaging of atherosclerotic plaque, reduced uptake by non-target tissues (liver), extended circulation, and carried antioxidant alpha-tocopherol to reduce oxidative burden in plaques. The method improves endothelial/plaque targeting by providing controlled distribution while also enabling researchers to control oxidative stress levels.

The nutraceutical nanoemulsions (curcumin, lycopene containing) protecting cardiomyoblasts against doxorubicin toxicity demonstrate their cardioprotective and antiarrhythmic potential through their ability to control oxidative stress and inflammation which results in decreased lipid peroxidation and decreased proinflammatory cytokine production but increased IL-10 levels. Formulations that are responsive to plaque microenvironment (high ROS / inflammation) release drug preferentially in plaques. The "Targeted nanoparticles triggered by plaque microenvironment" study (using Cur-loaded nanoparticles) showed that in Apoe-/- mice, the nanoparticle treatment reduces ROS, inflammatory marker expression, reduces plaque burden. While that study is of nanoparticles rather than strictly nanoemulsions, the mechanistic principle applies. Lipid nanoemulsions bearing anti-inflammatory agents to inflamed endothelium (e.g. the P-selectin targeting dexamethasone NE) show how endothelial targeting + anti-inflammatory action at the source reduces disease progression. Reviews of nanocarriers for vascular disease outline that various adhesion molecule targeting (ICAM-1, VCAM-1), selectins, and receptors overexpressed on activated endothelium or macrophages are being exploited for targeted delivery. Also, stimuli-responsive release (ROS, low pH etc.) are increasingly used in designs.

5. LIMITATIONS, GAPS, AND AREAS FOR FURTHER RESEARCH

While these mechanisms are promising, real-world translation is still limited; many studies are preclinical. Some gaps:

In vivo complexity: The in vivo environment is more complex: blood flow, shear stress, immune clearance, protein adsorption (opsonization), off-target uptake (e.g. by liver, spleen), which can reduce effective targeting or alter pharmacokinetics.

Stimuli specificity: Plaque microenvironment triggers (ROS, low pH, enzymes) are often heterogeneous. Designing release systems that respond to those triggers accurately without premature release elsewhere is challenging.

Safety of carriers / surface modifications: Ligands, antibodies, or coatings may themselves provoke immune response; long-term accumulation and toxicity of some nanomaterials (e.g. metal-based) needs careful evaluation.

Scaling / regulatory issues: Manufacturing reproducible, stable, safe nanoemulsions at scale; sterilization; shelf stability; cost; regulatory pathways.

Clinical evidence: There is still a paucity of large, randomized clinical trials showing that targeting, imaging, or antioxidant delivery via nanoemulsions truly change hard cardiovascular endpoints (e.g. myocardial infarction, mortality, stroke), rather than surrogate markers or experimental animal models.

Preclinical Evidence

In vitro studies on cardiovascular related cell lines

The nanoemulsions which contained anti-inflammatory nutraceuticals curcumin and tomato extract plus lycopene demonstrated their ability to decrease doxorubicin-induced cell death in cardiomyoblast H9C2 cells. The study showed ~35-40% improvement in cell viability over doxorubin alone. The study demonstrated that the test subjects exhibited lower lipid peroxidation through MDA and 4-HNA measurement plus they showed decreased pro-inflammatory cytokines through IL-6 and IL-8 and IL-1β and TNF-α assessment plus they showed decreased nitric oxide production and increased IL-10 levels. The study found that nanoemulsions had a size measurement which approximately reached 100 nanometers (Quagliariello et al., 2018). In Caco-2 cell lines (intestinal epithelial model), the nisoldipine nanoemulsion study showed enhanced uptake / absorption properties, better release in dissolution medium (in vitro diffusion) compared to the plain drug (Mundada et al., 2020).

Other studies of nanoemulsified curcumin (or "nano-curcumin") in vitro show suppression of NF-κB signalling, reduced macrophage migration, lowered TLR4 / RAGE expression, decreased MCP-1. For example, an NEC (nano-emulsion curcumin) in mice suppressed LPS-induced systemic inflammation via these pathways. While that is partly in vivo, the in vitro macrophage / human macrophage results also showed inhibited migration and inflammatory cytokine generation (Young et al., 2014). Transdermal nanoemulsions: e.g. carvedilol nanoemulsion for transdermal delivery showed improved permeation through rat skin compared to control / neat drug. This implies potential for bypassing oral route (Wang et al., 2008). These in vitro results establish improved solubility, better cellular uptake, stronger suppression of inflammatory or oxidative stimuli, and enhanced functional endpoints (viability, enzyme release, etc.).

Animal Studies in Hypertension, Atherosclerosis, Thrombosis etc.

A number of studies in animal models show that nanoemulsions or nano-formulations improve cardiovascular endpoints vs free drug or untreated controls.

Hypertension model: The study "Curcumin Nanoemulsion: Unveiling Cardioprotective Effects via ACE Inhibition and Antioxidant Properties in Hypertensive Rats" (DOCA-salt induced, uninephrectomized rats) showed that the curcumin nanoemulsion (abbreviated SNEC) significantly reduced elevated blood pressure, inhibited ACE activity, and reduced oxidative stress in hypertensive animals (Elbaset et al., 2022).

Diet induced metabolic / cardiovascular injury: The HFHF (high fat / high fructose) diet rat model: curcumin nanoemulsion at doses of 5 and 10 mg/kg (vs conventional CUR powder) given orally ameliorated hyperlipidemia, insulin resistance, and improved ECG changes; reduced markers of cardiac injury (troponin-I, creatine phosphokinase, lactate dehydrogenase), as well as restored liver enzyme (AST, ALT) levels; also improved markers of oxidative damage (e.g. 8-OHdG) and histopathology in heart, aorta, hepatic tissue. The higher nanoemulsion dose tended to perform better (Elbaset et al., 2022).

Enhanced antihypertensive drug delivery: The nisoldipine nanoemulsion study in rats: using nanoemulsion (globule size ~62 nm, PDI ~0.108, zeta potential ~ −26 mV) resulted in much higher in vitro release compared to plain drug dispersion. Pharmacodynamic studies in vivo in hypertensive rats showed significant decrease in blood pressure vs control, improved pharmacokinetics (higher absorption, likely via lymphatics) (Mundada et al., 2020). Other animal evidence: the "Oral Nanoformulations in Cardiovascular Medicine: Advances in Atherosclerosis Treatment" review outlines animal models where nanoemulsions or nano-carriers effectively delivered therapeutic agents, accumulated in plaque, reduced lesion size, etc. e.g. essential oils, compounds like curcumin, etc., in atherosclerotic mice (Sun et al., 2024). Also, in the cardiomyoblast nanoemulsion + doxorubicin model (though in vitro) but indicates the potential to protect heart tissue in vivo; some parts of that study plan to move into animal models (Quagliariello et al., 2018). These animal studies show benefits in multiple CVD-relevant domains: blood pressure control, lipid metabolism, oxidative stress, cardiac injury, histological damage, etc.

6. HUMAN CLINICAL TRIALS AND TRANSLATIONAL POTENTIAL

Research studies about human consumption show even fewer human studies than they actually perform because they do research on nutraceuticals. The randomized double-blind placebo-controlled trial tested 80 mg per day of nano-curcumin for 12 weeks with overweight and obese patients who had coronary slow flow phenomenon (CSFP) results showed better Seattle Angina Questionnaire scores in all areas which included physical limitation and angina stability and frequency/severity and treatment satisfaction and perception and quality of life than the placebo group. The nano-curcumin group showed significant improvements in triglycerides triglyceride/HDL-ratio and waist-triglyceride index and visceral adiposity index when compared to their baseline measurements. The current research study found that endocan and adropin and homocysteine showed no important changes (Rezaei et al., 2024). The clinical trial known as "Curcumin Nanomicelle Improves Lipid Profile Stress Oxidative Factors and Inflammatory Markers in Patients Undergoing Coronary Elective Angioplasty" used a randomized double-blind design to study 90 patients who received either 500 mg of curcumin or 80 mg of nano-curcumin or placebo during an 8 week period. The nano-curcumin group showed statistically significant improvements in total cholesterol and triglycerides and LDL when compared to control/placebo. The study "The Effects of Nano-Curcumin Supplementation on Risk Factors for Cardiovascular Disease: A GRADE-Assessed Systematic Review and Meta-Analysis" included randomized controlled trials about nano-curcumin which produced results showing improvements in glycemic profile because fasting glucose and insulin and HOMA-IR showed better results and HDL levels increased and lipid profiles improved especially in dyslipidemic people and CRP and IL-6 levels decreased and systolic blood pressure showed minor reductions (Helli et al., 2021). Translational potential: The review "Oral Nanoformulations in Cardiovascular Medicine: Advances in Atherosclerosis Treatment" discusses how nanoemulsions and nano-carriers are being engineered for oral use, using ligands, polymers, etc., to improve targeting, absorption, and plaque accumulation, with promising animal data (Ashtary-Larky et al., 2021). Thus, while human trials are small, relatively short duration, and often with nutraceuticals rather than "classical" cardiovascular drugs, the data so far support beneficial effects on surrogate markers: lipid profile, inflammation, endothelial dysfunction / angina symptoms, etc. (Paliwal et al., 2014).

Table-6.5 Preclinical and Clinical Evidence of Nanoemulsions in Cardiovascular Applications

Cell lines	Nanoemulsion / Formulation	Key Findings	Implications for CVD Therapy
In vitro (H9C2 cardiomyoblasts)	Curcumin / Lycopene NEs (~100 nm)	↑ Cell viability (~35–40%) vs doxorubicin; ↓ lipid peroxidation (MDA, 4-HNA); ↓ pro-inflammatory cytokines (IL-6, IL-8, IL-1β, TNF-α); ↑ IL-10	Protection against doxorubicin-induced cardiotoxicity; anti-inflammatory and antioxidant benefit
In vitro (Caco-2 cells)	Nisoldipine NE	↑ Uptake and absorption; improved in vitro release vs plain drug	Supports enhanced oral bioavailability of antihypertensive drugs
In vitro (macrophages,	Nano-curcumin (NEC)	Suppressed NF-κB signaling; ↓ TLR4 / RAGE; ↓ MCP-1; inhibited migration &	Anti-inflammatory, anti-atherosclerotic potential

human cells)		cytokine generation	
In vitro (rat skin model)	Carvedilol NE (transdermal)	Improved skin permeation vs neat drug	Possible alternative route for chronic antihypertensives
Animal (DOCA-salt hypertensive rats)	Curcumin NE (SNEC)	↓ Blood pressure; ↓ ACE activity; ↓ oxidative stress	Antihypertensive and cardioprotective effects
Animal (HFHF diet rats)	Curcumin NE (5–10 mg/kg oral)	Ameliorated hyperlipidemia & insulin resistance; improved ECG; ↓ cardiac injury markers (troponin-I, CPK, LDH); restored AST, ALT; ↓ oxidative stress (8-OHdG); improved heart/aorta/histology	Multi-organ protection; better than conventional curcumin
Animal (Hypertensive rats)	Nisoldipine NE (~62 nm, PDI 0.108, −26 mV)	↑ In vitro release; ↓ blood pressure; ↑ pharmacokinetic absorption (likely lymphatic)	Improved bioavailability and antihypertensive efficacy
Animal (atherosclerotic mice)	NE carriers with oils/curcumin	Accumulated in plaques; ↓ lesion size; improved plaque histology	Targeted atherosclerosis therapy
Human RCT (CSFP patients)	Nano-curcumin (80 mg/day, 12 wks)	Improved Seattle Angina Questionnaire scores; ↓ triglycerides, TG/HDL ratio, VAI, waist-TG index; no change in endocan, adropin, homocysteine	Symptomatic & metabolic improvements in coronary microvascular dysfunction
Human RCT (angioplasty patients, n=90)	Nano-curcumin (80 mg/day, 8 wks) vs curcumin 500 mg	↓ Total cholesterol, triglycerides, LDL; improved oxidative stress & inflammatory markers	Superior lipid-lowering & antioxidant benefit at lower dose
Human meta-analysis (RCTs)	Nano-curcumin (various doses/durations)	↓ Fasting glucose, insulin, HOMA-IR; ↑ HDL; ↓ CRP, IL-6; modest ↓ systolic BP	Systematic evidence for risk-factor modification in CVD
Review (translational)	Oral nanoformulations (ligand-functionalized, polymer-stabilized NEs)	↑ Targeting, absorption, plaque accumulation	Strong preclinical support for translation to clinical use

7. CHALLENGES AND LIMITATIONS

The process of transforming a nanoemulsion or nanoparticulate cardiovascular therapeutic from laboratory research into an effective product for medical use faces multiple challenges. The primary obstacle requires solutions for production processes to handle increased product volumes. The laboratory techniques which include ultrasonication and high-pressure homogenization and microfluidics and solvent displacement fail to translate into successful outcomes during large batch processing. Paliwal et al. describe the difficulty of maintaining droplet size and polydispersity index (PDI) and zeta potential throughout large volume production because even minor shear force and temperature and mixing and surfactant concentration alterations result in production differences between batches (Paliwal et al.,2014). Chatzidaki et al. point out that the main challenge of scaling nanoemulsions involves maintaining stability which includes preventing coalescence and Ostwald ripening and aggregation (Chatzidaki et al.,2025). At larger scales equipment limits which include pump pressures and mixing geometry together with heat dissipation and reproducibility of mixing dynamics become nontrivial. The removal or residual of organic solvents if using solvent displacement methods becomes more difficult during large-scale operations because Sánchez-López et al. explain that solvent elimination which occurs easily at milligram levels creates significant processing challenges at industrial operations (Sánchez-López et al.,2019). Process control and reproducibility become more difficult to achieve because functionalization (e.g. surface ligands and PEG and targeting moieties) together with coating steps (steric stabilization) introduce additional complexities (Kashyap et al., 2023).

The manufacturing process needs to solve the problem of maintaining long-term equipment storage. The nature of nanoemulsions allows them to maintain only their current kinetic state because they will reach thermodynamic equilibrium through time (Drais et al. 2015). The fresh batch shows excellent droplet uniformity but the droplet size distribution will change through the next several weeks and months because

surfactants will desorb and aggregation or sedimentation will take place. The Ostwald ripening process operates as a conventional destabilizing mechanism which causes smaller droplets to dissolve and redeposit their material onto larger droplets which leads to increasing droplet size throughout time (Ma et al. 2024). The delicate surfactant-oil-water balance becomes disturbed through temperature and ionic strength variations which happen during storage and transportation. Some emulsions show room temperature stability yet they experience reduced stability when exposed to refrigeration and freeze-thaw cycles and humidity changes. The formulation maintains its essential stability during dilution because the nanoemulsion remains stable in its undiluted state; however it will lose stability when diluted with plasma or other biological fluids. The research and development process together with quality control needs to solve a complex challenge which requires them to maintain product stability for six months to one year while controlling size and PDI and drug leakage and wettability.

The third area which needs attention requires examination of three elements which include safety and toxicity and biocompatibility. Nanoscale delivery systems enable better absorption and precise delivery and require smaller amounts of medication. Nanoparticles and nanoemulsions interact with biological systems in unanticipated ways through their protein adsorption process which creates a "protein corona" that leads to opsonization followed by mononuclear phagocyte system phagocytosis and the production of reactive oxygen species and membrane damage and the incorrect movement of substances to non-targeted tissues (Ahmad et al., 2022). Nanosystems exhibit high surface area and surface reactivity which results in their ability to experience complete operational changes from slight alterations in their diameter or electrical properties or physical configuration (e.g. cell uptake, inflammatory response) (Wolfram et al., 2015). The documented risks include hemolysis and complement activation and platelet aggregation and vascular endothelial damage and immune hypersensitivity. Sánchez-López et al. point out that large cationic nanoemulsions are more likely to cause hemolysis or erythrocyte damage, while opsonization can enhance clearance by macrophages, reducing the effective delivery to the target site. The authors of Wolfram et al. present a discussion about nanoparticle formulations which need to decrease their toxic effects while maintaining their ability to deliver therapeutic benefits. The persistent presence of some nanoparticles which appear to be safe can result in mitochondrial dysfunction and DNA damage and inflammation according to the research of (**Ahmad et al. 2022).** The discipline of precision nanotoxicology requires researchers to evaluate each nanostructure candidate through examination of its dosage, administration method, body distribution, biological processing, and eventual disposal methods. The process of long-term medication leads to two major safety issues which include toxic substance buildup in vital organs and the release of hazardous material through incomplete breakdown and hidden tissue swelling. Animal studies have demonstrated that nanoparticles can enter various organs where they remain for extended time periods which creates the risk of future health problems. The safety risks that manufacturing workers face during the processing of nano powders and the release of nanoparticle waste into water streams require urgent attention. (**Csoka et al., 2021**).

The regulatory environment exists in multiple jurisdictions which have not yet established rules to match the speedy development of nanomedicine research. Csóka and his colleagues present an extensive analysis of the regulatory processes which govern nano-based drug delivery systems, stating that authorities require scientists to present complete data about the substances physicochemical characteristics and their ability to repeatedly produce results and their effects on living organisms and their environmental impact and their potential to cause nanotoxicity before they grant permission to proceed (Csóka et al.,2021). The current regulatory systems which apply to traditional medications do not adequately address the distinct properties of nanomaterials, which forces officials to evaluate each situation through a specific procedure. Ventola states in the "The Nanomedicine Revolution" series that the FDA uses existing rules to regulate nanomedicines, but the agency needs to create new safety regulations for these products. The FDA requires manufacturers to submit new Investigational New Drug documentation when they change an approved pharmaceutical ingredient into a nanotechnology-based product **(Vosoughi et al.,2024).** Regulatory agencies such as the FDA and EMA mandate organizations to provide comprehensive proof which demonstrates that even small manufacturing changes by using different surfactants and changing mixing procedures will not affect product safety or effectiveness. The testing process requires regulators to obtain extensive data which includes in vivo

toxicology results and chronic exposure research along with immunogenicity tests and material degradation assessments and stability information because these studies require both financial resources and specialized knowledge. The classification problem creates additional difficulties because some nanomedicines exist at the boundary that separates drugs from biologics and medical devices which includes nano-carriers that possess imaging capabilities.

Figure- 6.4 Challenges and Limitations in Translating Nano-Based Cardiovascular Therapeutics

Regulatory authorities expect organizations to apply Quality by Design (QbD) because they need to identify essential product quality attributes and essential manufacturing process elements through risk assessment and process authentication for their production procedures. Csóka et al. emphasize employing a risk-based approach from early R&D to de-risk translation. The process of post-marketing surveillance necessitates mandatory implementation because actual toxic effects of nanomaterials will only emerge through extended usage in diverse populations. The regulatory framework requires continuous monitoring of real-world safety data and long-term studies which enable product usage suspension when safety issues arise. The research shows that nanoemulsion and nanoformulated cardiovascular treatments contain significant potential yet face serious development challenges before reaching clinical application. The process needs active teamwork among multiple disciplines to achieve three goals which include maintaining production consistency during scaling operations and creating products with long-lasting stability and safe biological compatibility that results in minimal health risks during extended usage while dealing with complicated government regulations. The development of nano-based therapies from initial testing to safe clinical use requires early identification of obstacles through the implementation of extensive design work combined with predictive toxicology studies and pilot production testing and ongoing communication with regulatory authorities.

8. FUTURE PERSPECTIVES

The next field of research for nanoemulsions aims to create intelligent systems that can detect and react to the specific microenvironmental changes associated with cardiovascular disease. The “on-demand”

formulations use local triggers to release their contents through controlled pH changes which occur in ischemic or inflamed tissues and through the detection of elevated reactive oxygen species (ROS) which exist in atherosclerotic plaques and through the enzymatic activity of matrix metalloproteinases and through the use of ultrasound light or magnetic fields. The use of stimuli-responsive strategies enables doctors to increase treatment effectiveness because they enable targeted drug delivery to areas with vascular damage and plaque-related inflammation while limiting patient exposure to drugs and their potential adverse effects. Researchers have proposed polymer- and lipid-based nanocarriers that use ROS or pH detection to deliver medication precisely to atherosclerotic lesions and ischemic myocardium which allows for controlled drug release during active disease periods while protecting against unwanted side effects. Designing such systems for oral nanoemulsions adds additional complexity (stability through the GI tract, absorption, and activation in the circulation or target site), but the concept has clear appeal for cardiovascular therapeutics where pathology is spatially and temporally heterogeneous. The recent studies and reviews about stimuli-responsive nano/bio-materials have created a comprehensive toolset of (pH, ROS, enzyme, thermal, and ultrasound-responsive chemistries) which can be used to enhance the precision of drug delivery systems and their control over drug delivery timing through their application to cardiovascular nanoemulsions.

The development of theranostic nanoemulsions which deliver therapeutic and diagnostic components through a single delivery system has emerged as a delivery method that works with "smart" delivery systems. The cardiovascular disease treatment employs nanoemulsions which deliver anti-inflammatory drugs and plaque-stabilizing medications together with MRI/CT/optical contrast materials, thus enabling doctors to track plaque distribution and measure treatment response in nearly real-time. The preclinical demonstration of theranostic platforms includes tests of macrophage-targeted anti-inflammatories and testing of iron-oxide or radionuclide-labeled particles for plaque imaging and therapy and the production of theranostic nanoemulsions which were developed for proof-of-concept studies. The method allows researchers to track biodistribution and accumulation through noninvasive means, which results in faster translational feedback loops because researchers can analyze failed therapeutic effects by checking delivery problems and clearing speed and payload size. The theranostic systems which use sensors like activatable fluorescent probes can monitor oxidative stress and enzymatic activity in lesions, so doctors can make treatment decisions based on biological results. The modern theranostic method supports precision cardiology because it has received positive results from preclinical tests and translational studies which focus on atherosclerosis and myocardial infarction and thrombosis (Sharma et al., 2023).

Personalized precision nanomedicine will become the most important area of growth which uses nanoemulsion design to develop treatments for individual patient biological needs. The treatment system needs to develop customized solutions through three different stages which include choosing specific ligands which will bind to the primary cell type found in a patient's lesions and choosing drug amounts according to their genetic profile and choosing excipients which will prevent allergic reactions in patients who have had previous reactions. Oncology precision methods have started testing phase because they can adapt to treat cardiovascular illnesses through patient stratification which uses plaque phenotype assessment and biomarker analysis and genetic dyslipidemia assessment to determine appropriate nanoemulsion combinations for each patient. The scientific progress of high-throughput assays and molecular imaging and systems pharmacology which includes PBPK modeling for nanoparticles will create faster in silico models which predict patient-specific nanoemulsion behavior thereby reducing clinical risks and guiding patient-specific dose adjustments. The implementation of precision nanomedicine in clinical settings needs interdisciplinary systems which connect diagnostic methods with formulation development and regulatory procedures but this approach will deliver better treatment results for patients with complex cardiovascular diseases.

The combination of nanoemulsion-based therapeutics with digital health solutions and nanotheranostics creates a powerful combination of technologies. The combination of digital tools combined with wearable sensors and remote monitoring and smartphone applications and cloud analytics and AI/ML models enables continuous monitoring of physiological data which includes heart rate variability and ambulatory blood pressure and ECG changes and activity levels to detect active disease periods when patients

experience unstable health. The combination of theranostic nanoemulsions with this system creates new operational processes which begin when sensors identify early plaque instability or ischemia and subsequently notify clinicians to either conduct their assessment or use automated decision support systems while administering a theranostic agent which can be triggered by focused ultrasound to produce subsequent imaging that verifies target engagement. AI systems developed through training on imaging data and digital biomarker information will enhance both patient selection and the prediction of responders and non-responders to particular nanoformulations which will result in improved adaptive dosing and more effective trial designs. The development of digital platforms enables researchers to conduct decentralized clinical trials while monitoring nano-therapies after their market introduction which enables them to detect uncommon or delayed adverse reactions that stem from the unique properties of nanomaterials. Early reviews of nanotheranostics emphasize the role of computational methods, mobile health integration, and real-time analytics in making personalized nanomedicine practical and scalable. The system requires successful integration through overcoming challenges which involve data interoperability and privacy issues and regulatory alignment for drug device software systems yet the project needs standardized interoperability and thorough clinical testing to achieve its goals.

The research shows promising results but two specific practical limitations reduce overall research expectations. The manufacturing process together with regulatory assessment of theranostic products becomes more difficult because of their dual function and their dynamic chemical properties; personalized nanoemulsions will increase regulatory scrutiny because each tailored variant could be viewed as a distinct product; and digital integration creates additional risks which include software reliability and cybersecurity problems that affect therapeutics. The initial achievements in developing theranostic nanoemulsions at larger production levels demonstrate their practical viability which requires engineering work and QbD analytics and direct communication with regulators to become successful. The most significant scientific breakthroughs will occur through small clinical updates which combine advanced nanoemulsions with specific diagnostic tools and digital decision-making systems instead of using entirely untested laboratory research methods. Smart nanoemulsions and nanotheranostics will revolutionize cardiovascular treatment into a system that provides precise medical care to treat critical health conditions through various stages of disease progression according to Liu et al. 2015.

Table-6.6 Future Perspectives of Nanoemulsions in Cardiovascular Therapy

Theme	Key Concept	Mechanism/Approach	Advantages	Challenges
Smart & Stimuli-Responsive Nanoemulsions	"On-demand" drug release	Triggered by pH shifts, ROS, enzymatic activity (MMPs), or external cues (ultrasound, light, magnetic fields)	Site-specific, temporally controlled release; reduced systemic toxicity	GI tract stability for oral delivery; complex design and activation mechanisms
Theranostic Nanoemulsions	Combined therapy + imaging	Dual payload: drug + contrast agent (MRI, CT, optical); sensors for enzymatic/ROS activity	Simultaneous treatment & monitoring; real-time feedback on delivery & efficacy	Manufacturing complexity; regulatory hurdles for dual-function systems
Personalized Nanoemulsions	Patient-tailored formulations	Ligand selection, drug payload adjustment, excipient optimization; PBPK modeling	Patient-specific targeting; minimized side effects; precision cardiology	Regulatory scrutiny (each variant = new product); requires advanced diagnostics
Integration with Digital Health & Nanotheranostics	Convergence of nanoemulsions + digital monitoring	Wearables, AI/ML models, mobile health platforms + theranostic imaging	Continuous disease monitoring; adaptive dosing; decentralized clinical trials	Data privacy, interoperability, software reliability, regulatory alignment
Translational Caveats	Practical considerations	Scale-up, regulatory engagement, Quality-by-Design (QbD), cross-	Feasible translation to clinic; incremental, robust	Complexity of chemistries; cybersecurity risks;

		disciplinary pipelines	clinical trials	high manufacturing costs

CONCLUSION

In conclusion, nanoemulsions represent a highly promising and versatile nanocarrier system for improving cardiovascular therapy by significantly enhancing the solubility and bioavailability of lipophilic drugs. The system enables drug delivery which targets specific areas in the body while delivering medications for an extended period together with decreased drug requirements to achieve medical results which correspond with conventional medical doses. The combination of better pharmacokinetic results and less frequent dosage requirements and better drug tolerability leads to improved patient compliance which plays an important role in managing cardiovascular diseases over time. Mechanistically, nanoemulsions demonstrate multiple beneficial effects through their endothelial targeting mechanism which releases drugs in a controlled manner while binding to atherosclerotic plaques and regulating oxidative stress and inflammatory pathways, which together enhance vascular health and prevent disease progression. Preclinical and limited clinical evidence further support their potential, demonstrating enhanced cellular protection, improved lipid profiles, and reduced cardiovascular risk markers. The successful clinical translation process needs researchers to analyze various formulation factors including droplet size and PDI and zeta potential and physiological stability together with the selection of safe biocompatible excipients. The process still needs to solve problems which involve manufacturing at large scales, obtaining regulatory approval, ensuring safety over extended periods, tracking drug interactions, and conducting clinical trials that include bigger groups of patients who have definite outcomes. The development of nanoemulsions continues through aggressive optimization which leads to evidence-based research that demonstrates their ability to transform cardiovascular medicine through innovative treatment methods that ensure patient safety and effectiveness.

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Authors' Contributions

All authors contributed equally to the conception, design, writing, and finalization of this work. Each author was actively involved in literature review, data interpretation, manuscript preparation, and critical revision. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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