



Palm Oil-Derived Lipid Nanocarriers for Controlled Drug Delivery: Advances in Nanostructured Lipid Carriers and Nanoemulsion Systems

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Abstract

Conventional drug delivery systems face persistent challenges, including poor aqueous solubility, suboptimal bioavailability, instability of therapeutic agents, and systemic adverse effects. Lipid-based nanocarriers have emerged as a transformative solution, and palm oil — a globally abundant, biocompatible, and Generally Recognized as Safe (GRAS)-classified vegetable oil — has attracted increasing pharmaceutical interest as a natural lipid matrix for these systems. This mini review synthesizes recent advances (primarily since 2020) in the design, fabrication, characterization, and biomedical application of palm oil-derived Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and nanoemulsion systems. Palm oil and its fractions — including palm stearin (solid lipid) and Palm Kernel Oil (PKO) (liquid lipid) — exhibit favorable lipid crystallinity, poly-morphic behavior, and fatty acid profiles that are advantageous for constructing stable nanocarrier matrices with controlled drug release kinetics. NLCs fabricated using palm stearin/PKO blends exhibit particle sizes below 200 nm, polydispersity indices below 0.3, and negative zeta potentials, indicating colloidal stability and enabling efficient encapsulation of diverse payloads, including hormonal drugs, antioxidants, and phytochemicals such as curcumin, lycopene, and β -carotene. Palm oil ester-based nanoemulsions further broaden the therapeutic repertoire, facilitating topical, oral, ocular, and pulmonary drug delivery. Despite compelling proof-of-concept data, challenges remain in scale-up manufacturing, long-term storage stability, regulatory approval pathways, and the integration of active targeting ligands. Future research should prioritize optimization of lipid composition, quality-by-design approaches, and in vivo efficacy validation to advance palm oil-derived nanocarriers towards clinical translation.

Keywords: Palm oil, Tocotrienol-rich fraction, Vitamin E, Chronic disease, Cardiovascular, Neuroprotection, Metabolic syndrome, Anticancer, Inflammation, Oxidative stress

JEL Classification Codes: I10; I12; I18; Q16; Q57

Introduction

The development of effective drug delivery systems remains one of the most pressing challenges in modern pharmaceutical science. A substantial proportion of newly synthesized therapeutic agents — estimates suggest 40–70% of drug candidates — exhibit poor water solubility and low oral bioavailability, limiting their clinical utility despite potent pharmacological activity. Conventional formulations often fail to protect labile drugs from gastrointestinal degradation, achieve targeted tissue distribution, or modulate release kinetics

in a therapeutically meaningful way, necessitating innovation in carrier design [1]. **Lipid-based nanocarrier systems**, including Solid Lipid Nanoparticles (SLNs), Nanostructured Lipid Carriers (NLCs), and nanoemulsions, have emerged as powerful platforms to address these limitations [2–4]. These systems exploit the inherent biocompatibility, biodegradability, and low toxicity of natural lipids to encapsulate hydrophobic, hydrophilic, and amphiphilic drugs, offering advantages such as enhanced drug solubilization, sustained-release profiles, improved mucosal permeability, and

protection of the encapsulated cargo from enzymatic and chemical degradation. Critically, among all nanoformulation categories, lipid-based nanoparticles are regarded as the least toxic for in vivo applications, with several formulations already achieving regulatory approval for clinical use [2,3,5-7].

Palm oil (*Elaeis guineensis* Jacq.) and its derivative fractions — primarily palm stearin (the high-melting solid fraction), palm olein (the liquid fraction), and Palm Kernel Oil (PKO) extracted from the kernel — represent a compelling and underutilized natural lipid resource for nanocarrier formulation. Palm oil is the world's most widely produced vegetable oil and is classified as a GRAS substance by regulatory agencies, providing a strong safety foundation for pharmaceutical use. Its unique fatty acid composition, dominated by palmitic acid (~44%) and oleic acid (~39%) in palm oil, and lauric acid (~48%) and myristic acid (~16%) in PKO, along with its documented lipid crystallinity and polymorphic behavior, makes it well-suited for constructing both solid and semi-solid lipid matrices in SLN and NLC systems. Palm Oil Esters (POEs), produced via enzymatic esterification of palm oil with fatty alcohols or polyols, further extend the palette of lipid excipients available for nanoemulsion platforms [8,9]. Despite a growing body of preclinical evidence and increasingly sophisticated formulation studies, the field of palm oil-derived lipid nanocarriers lacks a consolidated, critical synthesis of recent advances. This mini review aims to:

- Describe the lipid compositional properties of palm oil fractions relevant to nanocarrier design.
- Critically review SLN systems using palm-derived lipids, including preparation methods, characterization, and drug delivery applications;
- Examine NLC formulations employing palm stearin and PKO as binary lipid matrices;
- Analyze nanoemulsion systems based on palm oil and its esters;
- Address key challenges and future perspectives for clinical translation.

Lipid Composition of Palm Oil Relevant to Nanocarrier Formulation

The pharmaceutical utility of palm oil as a lipid matrix is fundamentally rooted in its distinctive fatty acid composition and molecular-level physical behavior. Palm oil is a semi-solid fat at ambient temperature owing to its approximately equal content of saturated and unsaturated fatty acids — principally palmitic acid (C16:0, ~44%) and oleic acid (C18:1, ~39%) — alongside minor proportions of linoleic acid (C18:2, ~10%) and stearic acid (C18:0, ~5%). This balance between saturated and unsaturated components underpins the polymorphic behavior critical for SLN and NLC performance, since lipid crystallinity directly governs

drug entrapment efficiency, release kinetics, and formulation stability over time [8,10,11]. Palm stearin, the high-melting solid fraction obtained by fractionation of palm oil, is particularly rich in palmitic acid (~57%) and is characterized by a high degree of crystallinity and a melting point of approximately 47–56°C, making it an ideal solid lipid matrix for SLN preparation. Its tightly packed crystalline lattice, however, can limit drug-loading capacity when used alone — a limitation addressed by combining it with liquid lipid components in an NLC architecture. Palm kernel oil, extracted from the endosperm of the palm fruit, is rich in Medium-Chain Triglycerides (MCTs) and high in lauric acid, conferring fluidity at physiological temperatures and excellent miscibility with surfactant systems; it serves as the liquid lipid component in binary NLC matrices. The juxtaposition of crystalline palm stearin and fluid PKO in NLC systems generates a disordered, amorphous lipid network with significantly more imperfections than pure solid lipid matrices, creating greater spatial accommodation for drug molecules and dramatically improving encapsulation efficiency compared with monolipid SLN systems [12,13]. From a regulatory perspective, both palm stearin and PKO are food-grade, GRAS-listed lipids with well-established safety profiles and minimal cytotoxicity in cell-based assays. Life-cycle assessments indicate that pharmaceutical-grade fractions can be obtained from existing industrial palm oil refining processes with minimal additional purification, supporting the techno-economic feasibility of large-scale nanocarrier manufacturing. The phytonutrient content of unrefined or minimally processed palm fractions — particularly tocotrienols, tocopherols, and β -carotene — may additionally confer antioxidant synergism within lipid nanocarrier matrices, potentially enhancing the shelf-life stability of encapsulated oxidation-sensitive drugs [6,8,14].

Solid Lipid Nanoparticles (SLNS) From Palm Oil

Solid Lipid Nanoparticles (SLNs) represent the first generation of lipid nanocarriers, comprising a solid lipid core stabilized by an emulsifying surfactant shell within an aqueous continuous phase, with typical particle sizes ranging from 50 to 400 nm. Compared with liposomes and polymeric nanoparticles, SLNs offer superior physical stability, greater scalability via high-pressure homogenization, and the ability to modulate drug release by manipulating lipid crystallinity and surfactant composition [4,6,13].

Palm stearin is among the most widely investigated natural solid lipids for SLN fabrication due to its favorable melting characteristics and compatibility with pharmaceutical surfactants such as Tween 80, Poloxamer 188, and soy lecithin [4]. Preparation methods employed for palm oil-based SLNs include:

- Hot High-Pressure Homogenization (hot HPH):** The drug-lipid melt is homogenized above the lipid melting point under high shear, producing uniformly sized nanodroplets that solidify on cooling; this is the most scalable method for industrial production [1].

b) Ultrasonication (Probe Sonication): High-intensity ultrasound disrupts the bulk lipid melt into nanosized particles; this method is more accessible at laboratory scale and allows fine-tuning of particle size through amplitude and duration settings [15].

c) Solvent Evaporation and Solvent Diffusion Methods: Organic solvent-based approaches offering precise control over particle morphology, though solvent residue management is a regulatory concern [1].

Studies examining palm stearin-based SLNs have reported particle sizes of 100–300 nm, Polydispersity Indices (PDI) below 0.3, indicating monodisperse distributions, and zeta potential values more negative than –20 mV, which are generally considered indicative of adequate colloidal stability. Drug entrapment efficiency (EE%) for hydrophobic payloads typically exceeds 70–85%, reflecting the affinity of lipophilic drugs for the solid lipid matrix [12]. In therapeutic applications, palm oil-derived SLNs have been explored for delivering anticancer agents, including curcumin, doxorubicin, and tyrosine kinase inhibitors, with studies reporting significant improvements in *in vitro* cytotoxicity and cellular uptake compared with free drug solutions [16]. SLN encapsulation of curcumin in solid lipid systems has been shown to elevate the compound's aqueous solubility by more than 10,000-fold and improve cellular permeation significantly. For oral delivery, palm oil-based SLNs improve gastrointestinal stability of drugs by shielding them from luminal pH changes and enzymatic hydrolysis, while promoting intestinal lymphatic transport, thereby bypassing hepatic first-pass metabolism for lipophilic drugs [17]. Topical formulations employing palm stearin SLNs exhibit favorable rheological profiles, good skin adherence, and sustained *in vitro* transdermal drug permeation, supporting their use in dermatological and cosmeceutical drug delivery [18]. A critical limitation of conventional SLNs is that lipid recrystallization during storage can lead to polymorphic transitions ($\alpha \rightarrow \beta \rightarrow \beta$ polymorphs), which may expel encapsulated drug molecules and cause drug leakage over time. This thermodynamic instability of SLNs in the β -polymorph drives interest in second-generation NLC systems that incorporate a liquid lipid component to deliberately disrupt crystalline order [19].

Nanostructured Lipid Carriers (NLCs) Using Palm Oil Fractions

Nanostructured Lipid Carriers (NLCs) represent a substantial advance over SLNs and are constructed from a binary lipid mixture of solid and liquid lipids, generating a partially amorphous, structurally disordered lipid core that greatly increases drug-loading capacity, reduces drug expulsion, and improves long-term stability. Palm stearin as the solid lipid and palm kernel oil (or palm olein) as the liquid lipid constitute a well-characterized, economically feasible, and biocompatible binary matrix that has been widely investigated in recent pharmaceutical literature [15].

A foundational study has developed an optimized NLC system for lynestrenol — a progestogen used in hormonal contraception — using a blend of Palm Stearin (PS) and Palm Kernel Oil (PKO) as the binary lipid matrix, prepared via high-shear homogenization followed by probe ultrasonication. The optimal formulation at a PS: PKO ratio of 6:4 (w/w), sonicated at 20% amplitude for 4.5 minutes without interval, yielded a particle size of 125.9 ± 3.24 nm, PDI of 0.21 ± 0.026 , and zeta potential of -29.87 ± 1.94 mV, meeting physicochemical criteria for a stable transdermal delivery system. These results confirm that the proportion of solid to liquid lipid critically determines particle architecture and that the PS/PKO system can be systematically optimized for a target nanocarrier profile [12].

Similarly, it has been investigated that NLC formation from a red palm oil (RPO)/palm stearin binary system has been investigated to deliver β -carotene, a lipophilic provitamin A carotenoid with antioxidant and immunomodulatory properties [20]. At an optimal RPO: palm stearin ratio of 5:5 (w/w), stable NLCs with favorable particle morphology, acceptable β -carotene content, and suitable optical properties were obtained, demonstrating that palm oil fractions with high bioactive content can serve dual roles as both lipid matrix and bioactive payload carrier. Furthermore, NLCs have been optimized using palm kernel stearin and rice bran oil as the lipid matrix for squalene encapsulation via ultrasonication, achieving particle sizes as small as 38.6 nm, PDI of 0.282, zeta potential of –34.1 mV, and encapsulation efficiency of 85.69% with minimal change after 28 days of storage, demonstrating excellent formulation stability [15].

NLCs from palm oil fractions have demonstrated utility across multiple delivery routes and payload types:

- a) Oral Delivery:** Palm oil-based NLCs enhance the gastrointestinal absorption of lipophilic bioactives through promotion of chylomicron assembly and intestinal lymphatic transport, bypassing first-pass hepatic metabolism [17].
- b) Transdermal Delivery:** The semi-solid nature of NLC films on skin creates an occlusive depot that enhances stratum corneum hydration and drug permeation, with palm stearin/PKO-derived NLCs demonstrating promising *in vitro* transdermal flux for steroid and anti-inflammatory drugs [19].
- c) Phytochemical Delivery:** NLC systems are particularly well-suited to encapsulate oxidation-sensitive phytochemicals such as curcumin, lycopene, quercetin, and tocotrienols, protecting them from chemical degradation during manufacturing and gastrointestinal transit while improving oral bioavailability [21].

Characterization of palm oil-derived NLCs typically employs Dynamic Light Scattering (DLS) to measure particle size and PDI, electrophoretic mobility measurements to determine zeta potential, Differential Scanning Calorimetry (DSC) to evaluate lipid

crystallinity and polymorphic state, and Transmission Electron Microscopy (TEM) for morphological assessment. Collectively, these parameters enable systematic formulation optimization and quality-by-design approaches for manufacturing [1,19,22].

Nanoemulsions Based on Palm Oil and Its Esters

Nanoemulsions (NEs) are isotropic, thermodynamically or kinetically stable colloidal dispersions of oil and water with droplet sizes typically in the range of 20–200 nm, stabilized by surfactant and co-surfactant systems. Their ultra-fine droplet size confers several pharmaceutical advantages over conventional emulsions, including enhanced drug solubilization, improved oral bioavailability through greater contact with the intestinal surface, augmented transdermal permeation, and protection of encapsulated molecules from oxidative and enzymatic degradation. Palm oil and Palm Oil Esters (POEs) — produced through enzymatic esterification of palm oil fatty acids with alcohols — have been explored as the oil phase in a range of biomedically relevant nanoemulsion platforms [9,23-25].

Pioneering work on palm oil ester nanoemulsions established their feasibility for topical drug delivery. Studies demonstrated that POE nanoemulsions formulated with Tween 80 as the surfactant and prepared by high-energy emulsification (probe ultrasonication or high-pressure homogenization) yielded droplet sizes below 100 nm for model anti-inflammatory drugs such as ketoprofen and ibuprofen, with excellent *in vitro* skin permeation profiles compared with conventional emulsions. Subsequent work explored incorporating hydrocolloid gums (e.g., xanthan gum) into palm kernel oil ester nanoemulsions to improve viscosity and mucoadhesion for enhanced topical delivery, reporting sustained drug release and significantly improved drug deposition within the skin layers [18,24,26-28]. In the context of anticancer drug delivery, quercetin-loaded Palm Oil Ester (POE) nanoemulsions have been developed for pulmonary administration, leveraging the aerosol-compatible viscosity and lung biocompatibility of POE systems to achieve targeted delivery to lung cancer cells via inhalation [16]. *In vitro* cytotoxicity studies confirm anti-tumor activity against lung carcinoma cell lines. The nanoemulsion droplet size, surfactant HLB, and drug-to-oil ratio critically govern both the aerodynamic properties and the drug-release behavior in pulmonary NE systems [9,26,29,30].

For oral delivery, palm oil-based nanoemulsions have demonstrated efficacy in improving the oral absorption of poorly water-soluble drugs and nutraceuticals [17]. The high interfacial area of nanoemulsion droplets facilitates rapid drug partitioning into the intestinal membrane, and the lipid phase of palm oil stimulates natural lymphatic transport pathways, particularly for long-chain triglyceride-based systems, resulting in significantly elevated plasma drug concentrations compared with aqueous drug suspensions. Red palm oil nanoemulsions and microencapsulated RPO formulations have been studied specifically for improving

the oral bioavailability of β -carotene and tocotrienols, with nanotechnology-based approaches consistently outperforming conventional oil-in-water emulsions in absorption metrics [9,31-33]. Regarding skin antiaging and cosmeceutical applications, palm oil-based nanoemulsions enriched with vitamin E and carotenoids from red palm oil serve simultaneously as delivery vehicles and bioactive agents, combining enhanced skin penetration with antioxidant protection against UV-induced oxidative damage. Preparation of these systems via low-energy spontaneous emulsification or Phase Inversion Temperature (PIT) methods is of interest for green manufacturing, though achieving consistent droplet sizes below 200 nm with high bioactive content without high-energy processing remains technically challenging [9,34-36].

Challenges and Future Perspectives

Despite the substantial pharmaceutical promise of palm oil-derived lipid nanocarriers, several interconnected challenges impede their clinical translation and require systematic investigation.

- a) **Scale-up and manufacturing reproducibility** represent perhaps the most immediate barrier. Laboratory-scale preparations using probe ultrasonication or bench-top homogenizers frequently produce particles with superior size distributions and loading efficiencies that are difficult to reproduce at pilot or commercial scale using continuous-flow high-pressure homogenizers, due to differences in shear geometry, heat transfer, and residence time distribution. Development of Quality by Design (QbD) frameworks incorporating Design of Experiments (DoE) methodologies is essential to identify critical material attributes (lipid ratio, surfactant concentration, aqueous phase composition) and critical process parameters (homogenization pressure, temperature, cycle number, sonication parameters) that collectively determine product quality [5,31,37,38].
- b) **Long-term physical and chemical stability** remains a significant concern. Palm oil-based SLNs are prone to lipid polymorphic transitions during storage, as they equilibrate toward the stable β -polymorph, leading to drug expulsion and aggregation. NLCs mitigate this through structural disorder but remain susceptible to Ostwald ripening or coalescence during prolonged storage, particularly under fluctuating temperatures. Regulatory guidelines require physicochemical stability data for 12–24 months under accelerated and long-term conditions before NDA submission, which represents a significant resource commitment for formulation development [39-42].
- c) **Active targeting and surface functionalization** present opportunities to enhance delivery specificity. The incorporation of Polyethylene Glycol (PEG) on the nanocarrier surface extends systemic circulation half-life by reducing opsonization and phagocytic clearance. Functionalization

with folic acid, transferrin, antibody fragments, or aptamers enables active targeting of tumor cells or inflamed tissues that overexpress specific receptors, thereby improving the therapeutic index of encapsulated drugs. For palm oil-derived NLCs carrying anticancer phytochemicals, active targeting could substantially improve on-target accumulation while reducing off-target toxicity, an area that warrants focused future investigation [16,21].

d) Regulatory and toxicological considerations also require attention. Although palm oil components are GRAS-classified and well-tolerated in food applications, the nanoparticulate form may exhibit distinct biodistribution, cellular uptake, and tissue accumulation compared with bulk lipids, necessitating dedicated nanotoxicological assessments. Regulatory agencies, including the FDA and EMA, have issued guidance on emerging topics in nanoformulation characterization and in vivo safety evaluation, requiring comprehensive data on genotoxicity, immunotoxicity, and organ-specific accumulation before clinical testing [7,43,44].

Looking ahead, the integration of stimuli-responsive design — incorporating pH-sensitive, thermosensitive, or redox-sensitive lipid components — into palm oil nanocarrier matrices represents a frontier approach to achieving on-demand drug release at target sites. Similarly, hybrid lipid-polymer nanoparticles that combine the biocompatibility of palm oil lipids with the structural tuneability of biodegradable polymers such as PLGA offer intermediate properties in stability, drug loading, and release control that may outperform either system alone [45-49].

Conclusion

Palm oil and its fractions — principally palm stearin, palm kernel oil, and palm oil esters — constitute a biologically compatible, economically accessible, and pharmaceutically versatile lipid resource for the construction of next-generation solid lipid nanoparticles, nanostructured lipid carriers, and nanoemulsion drug delivery systems. Their well-characterized fatty acid compositions, favorable polymorphism, and GRAS regulatory status provide a sound physicochemical and safety foundation for nanocarrier design. Experimental studies conducted since 2020 have demonstrated that palm oil-derived NLCs and SLNs can achieve clinically meaningful physicochemical attributes — particle sizes below 200 nm, PDI values under 0.3, zeta potentials exceeding -20 mV in magnitude, and encapsulation efficiencies above 80% — for diverse drug and bioactive payloads across oral, transdermal, and pulmonary delivery routes.

The critical path to clinical translation requires resolving persistent challenges in scale-up manufacturing, long-term stability, in vivo pharmacokinetic profiling, and regulatory compliance for nanoformulations. Prioritization of QbD-driven formulation strategies, integration of active targeting ligands, and

rigorous nanotoxicological assessment will collectively underpin the advancement of palm oil-derived nanocarriers from bench to bedside. Given the enormous global production infrastructure for palm oil and its fractions, successful pharmaceutical development of these systems could simultaneously support sustainable sourcing goals and broaden access to affordable nanomedicine platforms, particularly in palm oil-producing nations in Southeast Asia and West Africa.

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Conflict of Interest

None.

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