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Publications 2026

OPEN ACCESS
ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY (NIJPP)

Volume 7 Issue 1 Page 101-106, 2026

https://doi.org/10.59298/NIJPP/2026/71101106

Nanoparticle Encapsulated Artemisinin Derivatives for *Plasmodium falciparum*: Comparative Efficacy, Pharmacokinetics, and Resistance Prevention

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ABSTRACT

Malaria due to *Plasmodium falciparum* remains a major cause of morbidity and mortality, with an estimated 249 million cases and 608 000 deaths reported globally in 2022, and a high burden in sub–Saharan Africa. Artemisinin-based combination therapies (ACTs) are the cornerstone of treatment, but short drug half-lives, suboptimal exposure, and emerging artemisinin resistance threaten their long-term efficacy. This review evaluates nanoparticle (NP) encapsulated artemisinin derivatives as a strategy to improve antimalarial performance against *P. falciparum*. A narrative search of PubMed, Web of Science, and major organizational reports (WHO and MMV) from 2000 to 2025 identified primary preclinical studies, clinical reports, and key reviews on artemisinin chemistry, mechanisms, nanoparticle delivery systems, pharmacokinetics, and resistance. Evidence indicates that liposomes, polymeric nanoparticles, nanostructured lipid carriers, micelles, and inorganic platforms can increase apparent solubility, prolong circulation, enhance parasite killing in vitro and in vivo, and allow dose sparing compared with free drug. Encapsulation modifies absorption and distribution, supports controlled release, and may enhance drug exposure at the parasite niche while reducing off-target toxicity. Experimental models also suggest that higher and more sustained intra-parasitic exposure may limit survival of ring-stage-tolerant parasites and delay resistance selection. However, safety data are largely preclinical, and manufacturing, regulatory, and cost barriers remain substantial. Nanoparticle-encapsulated artemisinin derivatives are a promising adjunct to current ACTs, but rigorous translational pharmacology, scalable formulation, and well-designed clinical trials are required before broad implementation is feasible.

Keywords: artemisinin derivatives, nanomedicine, *Plasmodium falciparum*, pharmacokinetics, drug resistance

INTRODUCTION

Malaria remains one of the most important parasitic diseases worldwide, with above 240 million malaria cases and 627 000 deaths reported in 2020, with about 95% of the burden in the African Region, and *P. falciparum* is responsible for most fatalitiesM [1–3]. Artemisinin and its derivatives, including dihydroartemisinin (DHA), artemether, and artesunate, are fast-acting endoperoxide antimalarials that rapidly clear blood stage parasites and form the basis of ACTs recommended as first and second-line treatment for uncomplicated *P. falciparum* malaria [4].

Despite this success, several problems have emerged. Artemisinin derivatives have short plasma half-lives, variable oral bioavailability, and high first-pass metabolism, which may lead to subtherapeutic exposure in some patients [5]. Partial artemisinin resistance, characterized clinically by delayed parasite clearance and molecularly by kelch13 (K13) mutations, has now been documented in Southeast Asia and multiple African countries [6]. At the same time, health systems in endemic regions face challenges in ensuring adherence, maintaining the quality of oral formulations, and protecting partner drugs from resistance.

Nanoparticle-based drug delivery technologies offer a potential solution by improving solubility, stability, pharmacokinetics, and site-specific delivery of artemisinin derivatives. Recent reviews and experimental work have

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ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X
described diverse nanosystems, including liposomes, polymeric nanoparticles, lipid nanoparticles, and hybrid platforms encapsulating artemisinin and its derivatives for malaria therapy [7].

This review examines the scientific and translational rationale for NP encapsulated artemisinin derivatives in *P. falciparum* malaria. First, the chemistry, mechanisms of action, and limitations of artemisinin derivatives are summarized. Second, major NP platforms and encapsulation strategies relevant to antimalarial delivery are described. Third, comparative efficacy data in vitro and in vivo, including potency and dose sparing, are synthesized. Fourth, pharmacokinetics and biodistribution are considered in relation to treatment goals. Fifth, potential effects on resistance emergence are evaluated. Sixth, safety, toxicity, regulatory, and manufacturing considerations are discussed. Finally, clinical and public health perspectives are outlined, and priority directions for future research are proposed. The purpose is to provide a concise, mechanistically oriented appraisal of whether and how nanotechnology can extend the useful therapeutic life of artemisinin derivatives against *P. falciparum*.

Artemisinin derivatives: chemistry, mechanisms of action, and limitations

Artemisinin is a sesquiterpene lactone with a 1,2,4 trioxane endoperoxide bridge that is essential for antimalarial activity [8]. Semisynthetic derivatives such as DHA, artemether, and artesunate were developed to improve solubility and pharmacokinetic properties while retaining the endoperoxide pharmacophore. Artesunate is water-soluble and suitable for parenteral use, whereas artemether and DHA are more lipophilic and used in oral or intramuscular formulations.

Mechanistically, artemisinin derivatives are activated by ferrous iron or heme within the parasite food vacuole or cytosol, leading to cleavage of the endoperoxide bridge and generation of carbon-centered radicals and reactive oxygen species. These reactive intermediates alkylate multiple parasite proteins, damage membranes, and disrupt essential pathways, including hemoglobin digestion, redox homeostasis, and mitochondrial function [9]. Chemical proteomics suggests that artemisinin derivatives interact with a wide spectrum of targets enriched in parasite stress response and metabolic processes, supporting a pleiotropic mode of action [10].

However, important limitations constrain clinical performance. Artemisinin derivatives exhibit short elimination half-lives (approximately 1–3 h for DHA and artesunate) and rapid clearance, requiring combination with a longer-acting partner drug to prevent recrudescence [5]. They have poor aqueous solubility (especially artemisinin and artemether) and are subject to variable absorption and first-pass metabolism, contributing to high interindividual variability in exposure.

Partial resistance has emerged, characterized by reduced ring stage susceptibility and delayed clearance in vivo, rather than high-level failure at standard doses [11]. K13 propeller domain mutations and adaptive changes in stress response and DNA damage repair pathways underlie this phenotype. Artemisinin resistance threatens partner drugs, which then face higher parasite burdens and prolonged monotherapy exposure. These pharmacologic and evolutionary constraints motivate exploration of delivery strategies that increase and prolong intra-parasitic drug exposure without unacceptable toxicity.

Nanoparticle platforms and encapsulation strategies

Multiple NP platforms have been developed to encapsulate artemisinin derivatives and related antimalarials. Comprehensive reviews by Alven, Aderibigbe, and others summarize polymeric, lipid-based, and hybrid systems [7]. Liposomes, consisting of phospholipid bilayers surrounding an aqueous core, can incorporate both hydrophilic and lipophilic derivatives and are among the most advanced nanocarriers. Large unilamellar vesicles encapsulating artemisinin (ART LIPO) enhanced aqueous solubility and retained strong in vitro and in vivo antimalarial activity. Co-loading of artemisinin with curcumin or quercetin into specialized phospholipid vesicles (nutriosomes) has also been explored to exploit potential synergistic antimalarial and immunomodulatory effects [12, 13].

Polymeric nanoparticles, often based on polycaprolactone, polylactide, or chitosan, provide controlled release matrices for artemisinin derivatives. Polymer-based nanoformulations of artemisinin (ART PCL) achieved high entrapment efficiency and sustained drug release, and improved survival in *Plasmodium berghei*-infected mice when used alone or with classical antimalarials. Chitosan conjugates of DHA or DHA lumefantrine have also been proposed to enhance oral stability and mucosal uptake [14].

Lipid-based nanoparticles include solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Nanostructured lipid carriers formulated for intravenous artemether (Nanoject) employ a microemulsion template to generate sub 200 nm particles with high loading and controlled release; they aim to support parenteral treatment of severe malaria [15]. NLC co-loading artemether and lumefantrine for cerebral malaria therapy or for improved oral delivery represents another important class, enabling co-encapsulation of drugs with disparate solubilities.

Other platforms include inorganic or hybrid nanoparticles (for example, metal nanoparticles synthesized using plant extracts that carry artemisinin or act as intrinsic antiplasmodial agents) and micellar systems designed to solubilize highly hydrophobic derivatives [16]. Across platforms, key formulation goals are high encapsulation efficiency,

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ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

appropriate particle size (typically 50–200 nm), controlled release on the order of many hours, and acceptable colloidal stability in biologic fluids [17].

Comparative efficacy against *P. falciparum*: in vitro and in vivo

Encapsulation of artemisinin derivatives in nanoparticles generally preserves or enhances intrinsic antiplasmodial potency while modifying pharmacodynamic profiles. In RSC Advances, Valissery and colleagues demonstrated that artemisinin encapsulated in polycaprolactone nanoparticles or liposomes retained low nanomolar half maximal inhibitory concentrations (IC_{50}) against *P. falciparum* laboratory strains, comparable to ethanol solubilized free drug [18]. In a murine *P. berghei* model, both formulations achieved parasite clearance at total doses equivalent to or lower than free artemisinin, with the polymer formulation enabling prolonged survival and cure when combined with pyrimethamine or chloroquineb [5].

Liposomes co-loaded with artemisinin and curcumin exhibited superior in vitro activity compared with either agent alone, and improved in vivo parasite suppression, suggesting that co-delivery of a redox-active phytochemical may increase stress on parasite heme handling and redox pathways. Dimeric artesunate phospholipid conjugates formulated as liposomes showed enhanced potency in rodent malaria models, with lower effective doses and prolonged protection compared with conventional artesunate, likely due to increased membrane affinity and depot-like behavior [19].

NLC-based artemether formulations, such as Nanoject, achieved rapid parasite clearance in *P. berghei* models similar to that of conventional artemether injections, but at reduced doses and with extended intervals between injections. NLC co-loaded with artemether and lumefantrine improved survival and reduced recrudescence in cerebral malaria models, compared with separate administration of the free drugs, suggesting more synchronized pharmacokinetics of the two components [20].

It should be noted that much of the efficacy data derive from murine models using *P. berghei* or a few *P. falciparum* strains. Translational relevance is influenced by species differences in drug metabolism and parasite biology. Nonetheless, across studies, evidence indicates that nanoencapsulation can maintain low IC_{50} values, reduce total dose requirements, and extend the duration of parasite suppression, supporting a dose-sparing and potentially adherence-friendly strategy.

Pharmacokinetics and biodistribution

A central rationale for NP encapsulation is to optimize pharmacokinetics (PK) of artemisinin derivatives, which otherwise display rapid absorption and elimination with limited exposure. Conventional oral artemisinin and artemether show peak plasma concentrations within 1–2 h and are cleared within several hours, leading to a short area under the concentration time curve (AUC) and limited post treatment prophylaxis [21].

Nanostructured lipid carriers and liposomes can prolong circulation times by shielding the drug from immediate metabolism and by exploiting the enhanced permeability and retention effect in certain tissues. In the Nanoject artemether NLC study, intravenous administration yielded a biphasic PK profile with extended terminal half-life and higher AUC compared with an artemether solution, while maintaining acceptable clearance. Co-loaded artemether lumefantrine NLC demonstrated more synchronized plasma profiles of both components, with improved relative bioavailability and extended plasma residence, features that may support better partner drug protection.

Artemisinin nanoformulations, such as ART PCL nanoparticles and ART LIPO liposomes, increased apparent solubility and provided prolonged release in vitro, with sustained plasma concentrations in mice and delayed elimination compared with free artemisinin [22]. Biodistribution studies suggest that many lipid-based nanoparticles accumulate in the mononuclear phagocyte system (liver, spleen), which is also a key site of parasite sequestration, potentially enhancing exposure at parasite-laden tissues.

However, few studies have quantified drug levels within infected erythrocytes or at microvascular sites where sequestration occurs, and scaling from rodents to humans remains uncertain. Reviews emphasize the need for integrated PK–pharmacodynamic modeling incorporating nanoparticle disposition, drug release kinetics, and parasite stage specificity [23]. Overall, available data indicate that NP encapsulation can increase AUC, extend apparent half-life, and favor tissue distributions relevant to malaria pathophysiology, all of which support exploration in human studies.

Resistance emergence and prevention

Artemisinin resistance in *P. falciparum* is linked to K13 mutations, ring stage quiescence, altered redox and proteostasis pathways, and enhanced DNA damage repair [24]. Clinical and genomic data show that partial resistance has independently emerged in Southeast Asia and Africa, including in Uganda, and is associated with longer parasite clearance times and increased ACT failure when partner drug resistance is also present [25].

Nanoparticle delivery could influence resistance dynamics through several mechanisms. First, sustained drug release and higher minimum concentrations may reduce windows of sublethal exposure that permit survival of quiescent

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ONLINE ISSN: 2992-5479
PRINT ISSN: 2992-605X

ring stages; modeling suggests that maintaining concentrations above a threshold during the ring to trophozoite transition is critical [26]. Second, co-encapsulation of artemisinin derivatives with partner drugs may enforce more consistent combination ratios in plasma and within infected cells, reducing effective monotherapy exposure when one drug clears more rapidly than the other. Third, targeted delivery to infected erythrocytes or sequestration sites could increase parasite-specific drug levels, allow shorter overall courses while maintain curative exposure.

Direct experimental evidence linking NP based formulations to reduced resistance selection is limited. In murine models, polymeric artemisinin nanoparticles in combination with older antimalarials delayed recrudescence and extended cure rates compared with free combinations, which indirectly suggests less opportunity for resistant parasites to emerge. At the population level, resistance evolution is shaped by transmission intensity, drug pressure, and health system performance [27]; improved adherence and more reliable exposure achieved via long-acting nanoformulations might contribute to lower selection pressure from underdosing.

Conversely, persistent low-level drug release from long-circulating nanoparticles could, in principle, create extended periods of subtherapeutic exposure. Hence, careful design of release profiles and dosing regimens, aligned with parasite life cycle dynamics and partner drug kinetics, will be critical. Current evidence supports the hypothesis that well-designed NP systems could help delay, but not abolish, artemisinin resistance.

Safety, toxicity, and translational considerations

Artemisinin derivatives have a favorable therapeutic index in conventional formulations, with extensive clinical data in adults, children, and pregnant women beyond the first trimester [28]. Nanoparticle encapsulation introduces new safety dimensions related to carrier composition, size, surface charge, and biodistribution. Preclinical studies of artemisinin, artemether, or artesunate in liposomes, polymeric nanoparticles, and NLC have generally reported acceptable acute toxicity, with no major histopathologic abnormalities at therapeutic dose ranges in rodents.

Nevertheless, many nanocarriers accumulate in the liver and spleen and may induce complement activation, oxidative stress, or immunomodulation, especially upon repeated dosing. Cationic or inorganic particles can be more reactive and warrant careful evaluation. Chronic toxicity, reproductive toxicity, and potential interactions with co-administered vaccines or antiretrovirals remain poorly characterized.

From a regulatory perspective, only a limited number of nanoformulated small molecule drugs have been approved globally, mostly liposomal or albumin-bound anticancer agents. Regulatory agencies require robust characterization of particle properties, stability, and release kinetics, as well as validated manufacturing processes following good manufacturing practice [17]. For malaria, additional expectations include heat stability, compatibility with existing supply chains, and cost appropriate to low-resource settings.

Manufacturing challenges are substantial. Many sophisticated NP formulations rely on organic solvents, complex multi-step processes, or cold chain storage, which can raise costs and limit accessibility. Advances in scalable methods, such as high-pressure homogenization or microfluidic mixing, and the use of pharmaceutically established excipients, will be essential for translation [18]. Overall, available data indicate that artemisinin nanoformulations can be engineered with acceptable short-term safety in animals, but comprehensive toxicology and early-phase clinical trials are required before use in vulnerable populations such as children and pregnant women.

Clinical and public health perspectives and future research directions

At present, no NP encapsulated artemisinin derivative has reached routine clinical use, and ACTs remain the standard of care [29]. Several translational scenarios can be envisaged. One is parenteral NLC or liposomal formulations of artemether or DHA lumefantrine for severe malaria or for patients unable to tolerate oral therapy, potentially providing a rapid onset with prolonged coverage compared with artesunate alone. Another is long-acting injectable or implantable NP systems that deliver both an artemisinin derivative and partner drug over several days, which could simplify directly observed therapy and reduce the risk of incomplete courses.

In endemic settings with constrained health systems, the public health impact of such technologies will depend on affordability, ease of administration, compatibility with community-based treatment models, and acceptability to patients and providers. Integration with emerging tools such as malaria vaccines and triple ACTs may be necessary to counter rising resistance [30].

Future research priorities include: (i) rational design of targeted nanoparticles that recognize infected erythrocytes or parasite derived ligands, thereby enriching drug at sites of sequestration; (ii) systematic PK–pharmacodynamic studies in relevant animal models and, ultimately, in humans to define optimal release profiles and dosing regimens; (iii) co encapsulation strategies for artemisinin derivatives with existing partners (for example lumefantrine, piperaquine) or with new agents, engineered to align elimination half-lives; (iv) robust evaluation of immunologic and off target effects, particularly in populations with comorbid infections or malnutrition; and (v) development of cost effective, thermostable formulations that can be manufactured and distributed at scale in low and middle income countries.

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PRINT ISSN: 2992-605X

If these challenges are addressed, NP encapsulated artemisinin derivatives could contribute to a next generation therapeutic armamentarium for malaria, complementing vector control, vaccination, and surveillance for resistance markers.

CONCLUSION

Artemisinin derivatives remain central to the treatment of *P. falciparum* malaria but are constrained by short half-lives, variable exposure, and the emergence of partial resistance linked to K13 mutations and ring stage tolerance. Nanoparticle encapsulation offers a mechanistically attractive strategy to address these limitations by enhancing solubility, prolonging circulation, and improving delivery of artemisinin derivatives and their partner drugs to parasite-infected compartments. Preclinical data from liposomal, polymeric, and lipid-based systems consistently show preserved or improved in vitro potency, dose sparing in vivo, extended pharmacokinetics, and encouraging safety profiles in animal models. Conceptually, long-acting and co-encapsulated nanoformulations could reduce the probability of inadequate artemisinin exposure, improve partner drug matching, and thereby help delay further resistance evolution. However, the current evidence base is dominated by small laboratory studies, often in rodent malaria models, with heterogeneity in formulations, endpoints, and quality. Critical knowledge gaps include human pharmacokinetics, interindividual variability, immunologic responses to nanocarriers, and the feasibility of large-scale manufacture at costs compatible with endemic settings. Translational progress will require interdisciplinary collaboration between medicinal chemists, formulation scientists, clinicians, and policymakers, as well as alignment with global malaria control priorities. NP encapsulated artemisinin derivatives should be advanced through prioritized preclinical standardization and early phase clinical studies, with a strategic focus on formulations that demonstrably improve exposure–response relationships while remaining affordable and scalable for high burden malaria settings.

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CITE AS: Nambi Namusisi H. (2026). Nanoparticle Encapsulated Artemisinin Derivatives for Plasmodium falciparum: Comparative Efficacy, Pharmacokinetics, and Resistance Prevention. NEWPORT INTERNATIONAL JOURNAL OF PUBLIC HEALTH AND PHARMACY,7(1):101-106. https://doi.org/10.59298/NIJPP/2026/71101106