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

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ABSTRACT

Artemisinin derivatives are the backbone of current malaria therapy, yet *Plasmodium falciparum* resistance threatens global control efforts. Poor solubility, short half-life, and suboptimal tissue distribution limit their efficacy. Nanoparticle encapsulation offers potential to enhance drug delivery, improve pharmacokinetics, and reduce resistance emergence. This review evaluated nanoparticle-encapsulated artemisinin derivatives, comparing efficacy, pharmacokinetics, and resistance prevention potential against *P. falciparum*. Literature was retrieved from PubMed, Web of Science, and Scopus 2010-2025 using search terms "artemisinin," "nanoparticle," and "Plasmodium falciparum," focusing on comparative preclinical and clinical data. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, and nanocrystals have demonstrated improved solubility, prolonged circulation, and enhanced bioavailability. Encapsulation consistently increased in vitro and in vivo parasite clearance rates compared to free drug, with some formulations achieving extended half-life by two- to threefold. Pharmacokinetic benefits included sustained plasma concentrations above minimum inhibitory levels and improved distribution to infected erythrocytes. Several studies suggest reduced selection for resistant strains, potentially through sustained exposure and complete parasite clearance. Safety profiles are generally favorable, though long-term toxicity and large-scale production challenges remain. Nanoparticle-based artemisinin delivery holds promise for optimizing therapeutic efficacy and delaying resistance in *P. falciparum*. Further clinical validation, stability optimization for endemic settings, and cost-effective manufacturing are priorities to enable translational impact.

Keywords: Artemisinin derivatives, Nanoparticle delivery, *Plasmodium falciparum*, Pharmacokinetics, Resistance prevention.

INTRODUCTION

Malaria caused by *Plasmodium falciparum* remains a major public health concern, with over 240 million cases and significant mortality annually [1, 2]. Artemisinin derivatives such as artesunate, artemether, and dihydroartemisinin form the core of artemisinin-based combination therapies (ACTs), recommended by the World Health Organization for first-line treatment [3, 4]. Their rapid parasite clearance, broad activity across blood stages, and established clinical safety underpin their global use. However, emerging *P. falciparum* resistance, particularly in Southeast Asia and increasingly in Africa, poses a critical threat to treatment efficacy and control efforts [5, 6]. Resistance is often associated with delayed parasite clearance and mutations in the *kelch13* propeller domain. Pharmacological limitations contribute to resistance selection. Artemisinin derivatives are poorly water soluble, have short elimination half-lives (typically <1.5 hours), and require partner drugs for sustained efficacy [7, 8]. These properties can result in subtherapeutic concentrations, particularly in poorly perfused tissues, enabling survival of less susceptible parasites. Interindividual pharmacokinetic variability, driven by metabolism, nutrition, and comorbidities, further complicates optimal exposure.

Nanoparticle encapsulation offers a promising approach to address these limitations. Nanocarriers can improve solubility, protect labile drugs from degradation, enhance absorption, prolong systemic circulation, and enable targeted delivery to infected erythrocytes or specific tissues [9, 10]. Platforms such as liposomes, polymeric

nanoparticles, solid lipid nanoparticles, and drug nanocrystals have been explored for artemisinin delivery. By enhancing pharmacokinetic profiles, nanoparticle-based formulations may sustain drug concentrations above inhibitory thresholds, improving parasite clearance and potentially limiting the survival of resistant subpopulations. Additionally, controlled release profiles may reduce dosing frequency, improving adherence in resource-limited settings. This review synthesizes current evidence on nanoparticle-encapsulated artemisinin derivatives, with emphasis on comparative efficacy, pharmacokinetic enhancements, and resistance prevention. It also examines safety considerations, translational challenges, and research priorities necessary to realize the potential of these advanced drug delivery systems in malaria-endemic regions.

Overview of Artemisinin Derivatives and Mechanisms of Action

Artemisinin and its semi-synthetic derivatives exert potent antimalarial activity through activation of their endoperoxide bridge by ferrous iron, abundant in parasite-infected erythrocytes [11, 12]. This activation generates reactive oxygen species and carbon-centered radicals that alkylate parasite proteins and lipids, disrupting vital functions. Artemisinins rapidly reduce parasite biomass but are cleared quickly from plasma, necessitating combination therapy with longer-acting partner drugs.

Nanoparticle Platforms for Artemisinin Delivery

i. Liposomes are phospholipid vesicles capable of encapsulating both hydrophilic and lipophilic drugs [13, 14]. They can improve stability, enable sustained release, and target macrophage-rich organs.
ii. Polymeric nanoparticles (e.g., poly(lactic-co-glycolic acid), chitosan) offer controlled release and tunable surface properties for targeted delivery [15].
iii. Solid lipid nanoparticles combine the advantages of liposomes and polymeric carriers, providing stability and high drug loading for lipophilic compounds.
iv. Nanocrystals are pure drug particles reduced to nanoscale, enhancing dissolution rates and bioavailability without complex excipients.

Comparative Efficacy Against *P. falciparum*

Encapsulation of artemisinin derivatives has consistently improved in vitro potency against both sensitive and resistant *P. falciparum* strains [16, 17]. In murine malaria models, liposomal artesunate reduced parasitemia more rapidly and sustained suppression longer than free artesunate. Polymeric formulations of artemether achieved higher survival rates and delayed recrudescence. Solid lipid nanoparticles delivering dihydroartemisinin showed enhanced brain penetration in cerebral malaria models, improving survival [18, 19]. Nanocrystals of artemisinin improved oral bioavailability, leading to higher peak plasma concentrations and faster parasite clearance.

Pharmacokinetics and Biodistribution Comparisons

Nanoparticle encapsulation typically increases half-life by 2–3 times, reduces clearance rates, and sustains plasma drug concentrations above the minimum inhibitory concentration [20]. Biodistribution studies indicate improved uptake in the liver and spleen, aligning with parasite sequestration sites. Lipid-based carriers preferentially associate with infected erythrocytes, potentially enhancing targeted delivery. Polymeric carriers offer the advantage of customizable release kinetics to match parasite life cycles.

Role in Resistance Prevention

Sustained therapeutic concentrations reduce the window of subtherapeutic exposure that fosters survival of partially resistant parasites [21, 22]. Some in vitro studies suggest nanoparticle delivery can overcome modest reductions in artemisinin susceptibility by ensuring prolonged intracellular exposure. By reducing parasite recrudescence and residual parasitemia, these systems may limit selection pressure for resistant phenotypes. However, definitive evidence from field studies is lacking.

Safety, Toxicity, and Translation Challenges

Preclinical toxicity studies generally show good tolerability, with transient liver enzyme elevations or mild inflammatory responses in some polymeric formulations. The long-term safety of chronic nanoparticle exposure in endemic populations remains uncertain [23]. Translation challenges include scale-up manufacturing, cost-effectiveness, and stability under tropical conditions. Regulatory pathways for complex formulations may require additional pharmacokinetic and toxicological data.

Future Directions and Research Gaps

Further work should prioritize thermostable, low-cost nanoparticle formulations suitable for mass production and distribution in endemic regions [24]. Clinical trials are needed to confirm efficacy gains, pharmacokinetic advantages, and resistance prevention in humans. Integration with ACT regimens, evaluation in high-transmission settings, and community acceptability studies will be critical for successful adoption.

Table 1: Comparative summary of key formulations

Platform	Drug loading (%)	Release profile	Half-life extension	Efficacy gain vs free drug	Resistance impact
Liposomes	20–35	Sustained (24–72 h)	2–3×	Faster clearance, less recrudescence	May reduce resistant strain survival
Polymeric nanoparticles	15–30	Controlled (48–96 h)	2–3×	Higher survival in models	Potentially delays resistance emergence
Solid lipid nanoparticles	25–40	Sustained (24–72 h)	2–2.5×	Improved brain penetration	Reduced recrudescence in cerebral malaria
Nanocrystals	90–100	Rapid dissolution	1.5–2×	Higher Cmax, faster clearance	Limited evidence

CONCLUSION

Nanoparticle encapsulation of artemisinin derivatives represents a significant advance in malaria pharmacotherapy, with potential to address key limitations of current formulations. By enhancing solubility, prolonging systemic circulation, and improving tissue targeting, nanoparticle systems can increase drug exposure at parasite sequestration sites and maintain concentrations above inhibitory thresholds. Preclinical evidence demonstrates superior parasite clearance, reduced recrudescence, and potential mitigation of resistance development compared with free drugs. However, the promise of these systems is tempered by translation challenges. Manufacturing scalability, cost, and stability under field conditions remain critical barriers to implementation in endemic settings. Comprehensive toxicological evaluation and well-designed clinical trials are required to validate safety and efficacy in diverse populations, including children and pregnant women. Strategic integration of nanoparticle formulations into ACT regimens, coupled with optimized dosing to leverage pharmacokinetic benefits, may strengthen first-line therapies and extend their useful lifespan. Collaboration between researchers, industry, and global health agencies will be essential to advance these technologies from laboratory to field. With targeted research addressing operational, regulatory, and economic challenges, nanoparticle-encapsulated artemisinin derivatives could become a cornerstone in the fight against *P. falciparum*, offering enhanced efficacy and a pragmatic tool for resistance management.

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