International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Role of Nanotechnology in Enhancing Therapeutic Efficacy and Pharmacokinetic Profiles for Dengue

Mr. Abisesh Muthusamy[1], Dr. Vinayak Mastiholimath[2]

[1]PG Student, [2]Professor
[1, 2]KLE College of Pharmacy, Belagavi, Karnataka

Abstract

Dengue virus (DENV) infection remains one of the world's most pervasive mosquito-borne threats, with nearly 390 million infections annually and approximately 96 million clinically apparent cases[1]. Despite this enormous burden, there are no approved antivirals with both potent efficacy and favorable pharmacokinetics. Nanotechnology-based delivery systems have emerged as powerful platforms to overcome traditional drug-delivery barriers—poor solubility, rapid degradation, off-target toxicity—by modulating drug physicochemistry, enhancing bioavailability, enabling precise targeting, and providing controlled release. Here, we comprehensively review advances in lipid-, polymer-, and inorganic-based nanocarriers for dengue therapy, focusing on eleven major classes: phytosomes, liposomes, cubosomes, niosomes, ethosomes, transfersomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, polymeric micelles, nanoemulsions, and nanocrystals. For each, we detail composition and preparation, physicochemical characterization, mechanisms of cellular uptake and endosomal escape, multimodal antiviral and immunomodulatory actions, and quantitative pharmacokinetic improvements—including extended circulation, sustained release, and lymphatic uptake. Preclinical efficacy in dengue models is summarized alongside immunotoxicity, biodistribution, and regulatory considerations. Finally, we outline future directions in personalized and theranosticnanomedicines tailored to patient-specific viral and immunological profiles.

Keywords: Dengue, Nanocarriers, Bioavailability, Targeted Delivery, Pharmacokinetics, Controlled Release, Phytosomes, Liposomes, Dendrimers

1. Introduction

1.1 Global Burden and Unmet Need

Dengue virus (DENV) is an enveloped, positive-sense RNA flavivirus transmitted primarily by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Over the past half-century, its geographic range has expanded dramatically, fueled by urbanization, global travel, and climate change that broadens the mosquitoes' habitable zones. It is now endemic in more than 100 tropical and subtropical countries, placing nearly half the world's population at risk. The World Health Organization estimates roughly 390 million infections annually, of which approximately 100 million manifest clinically[1,2,3]. Clinical presentations range from undifferentiated fever to classic dengue fever—characterized by high fever, severe myalgia, arthralgia, and rash—to life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome

(DSS). In DHF/DSS, increased vascular permeability leads to plasma leakage into third spaces, resulting in hemoconcentration, bleeding diatheses, and hypovolemic shock; case fatality rates can exceed 20 % without prompt fluid management and critical care support[3].

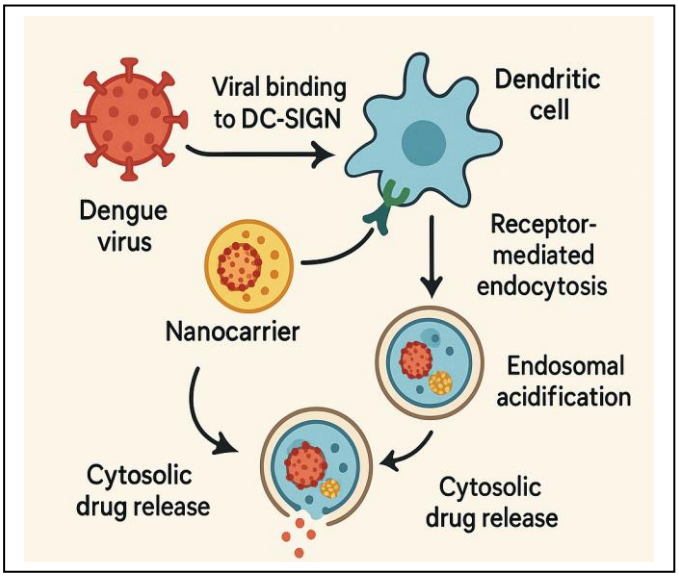
Despite intensive research into small-molecule antivirals, no specific treatment has been approved; current management is entirely supportive, focusing on judicious fluid resuscitation, hemodynamic monitoring, and treatment of complications such as hemorrhage or organ dysfunction. In resource-limited endemic regions, the strain on healthcare systems is severe during outbreaks, overwhelming hospital capacity and driving high morbidity and mortality[4].

1.2 Limitations of Conventional Antivirals

Efforts to develop direct-acting antivirals for DENV have centered on small molecules that inhibit virus-host receptor interactions, viral RNA polymerase, protease NS2B-NS3, or host factors critical for replication. However, these candidates frequently confront fundamental biopharmaceutical hurdles. Many exhibit poor aqueous solubility that limits gastrointestinal dissolution and hence oral bioavailability. Once absorbed, they may undergo extensive first-pass metabolism by cytochrome P450 enzymes and phase II conjugating enzymes, substantially reducing systemic exposure. Moreover, efflux transporters such as P-glycoprotein in enterocytes and hepatocytes actively pump substrate drugs back into the gut lumen or bile, forcing higher dosing to achieve therapeutic plasma concentrations. These high doses in turn amplify the risk of off-target toxicity—particularly hepatotoxicity and nephrotoxicity—which is of acute concern in dengue patients experiencing compromised organ perfusion due to plasma leakage and shock[5,6].

Beyond ADME (absorption, distribution, metabolism, excretion) limitations, many antivirals distribute non-selectively, exposing healthy tissues and exacerbating systemic side effects. For instance, hepatic accumulation can provoke transaminase elevations, while renal excretion of toxic metabolites may precipitate acute kidney injury. In severe dengue, organ dysfunction further impairs drug clearance, creating a vicious cycle of toxicity and therapeutic failure.

1.3 Nanotechnology as a Transformative Strategy



(Fig.1 Dengue virus binds to DC-SIGN on dendritic cells, triggering receptor-mediated endocytosis. Within the acidified endosome, pH-sensitive or "proton–sponge" nanocarriers release their antiviral payload into the cytosol, enhancing intracellular delivery and efficacy)

Nanotechnology offers a platform to circumvent these obstacles by packaging drugs within carriers sized 1–200 nm, thereby tuning physicochemical properties and biodistribution. Lipid-based systems (liposomes, solid lipid nanoparticles, cubosomes), polymeric nanoparticles (PLGA, dendrimers, micelles), and inorganic nanostructures (gold, silica) each afford distinct advantages:

Enhanced Solubility & Stability: Hydrophobic antiviral compounds can be sequestered in lipid bilayers or polymer cores, shielding them from aqueous environments and gastrointestinal degradation. Labile biologics (siRNA, peptides) gain protection from nucleases and acidic pH.

Prolonged Circulation: Grafting polyethylene glycol (PEG) onto the nanoparticle surface generates a hydrophilic "stealth" brush that resists protein adsorption (opsonization) and subsequent clearance by the mononuclear phagocyte system (MPS), extending plasma half-lives from minutes to hours or even days[8,9].

Targeted Delivery: Passive targeting exploits the enhanced permeability and retention (EPR) effect in inflamed or highly vascularized tissues, while active targeting incorporates ligands—monoclonal antibodies or scFv against DENV envelope protein, mannose for C-type lectin receptors on dendritic cells—to direct nanoparticles to virus-infected cells, thus concentrating the drug at the site of infection and sparing healthy tissues.

Controlled Release: Biodegradable polymers (e.g., PLGA) permit fine tuning of drug release kinetics through manipulation of polymer composition (lactic\:glycolic ratio), molecular weight, and particle size, enabling sustained therapeutic levels over days to weeks and reducing dosing frequency. Stimuli-responsive materials (pH-sensitive lipids, redox-labile linkers) trigger on-demand drug release within acidic endosomes or the high-glutathione intracellular milieu.

Endosomal Escape: "Proton-sponge" polymers (polyethylenimine, chitosan) and fusogenic lipids (dioleoylphosphatidylethanolamine derivatives) destabilize endosomal membranes via osmotic swelling or lamellar-to-hexagonal phase transitions, respectively, facilitating cytosolic delivery of nucleic acids or small molecules.

In the sections that follow, we analyze eleven representative nanocarrier platforms—phytosomes, liposomes, cubosomes, niosomes, ethosomes, transfersomes, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, polymeric micelles, Nano emulsions, and Nano crystals—detailing their formulation strategies, mechanistic underpinnings of cellular uptake and cargo release, pharmacokinetic advantages, and efficacy in preclinical dengue models, as well as considerations for safety, bio distribution, and clinical translation.

2. Nanocarrier Platforms for Dengue Therapy

2.1 Phytosomes

Phytosomes are molecular complexes formed by noncovalent hydrogen bonds and π–π stacking between phytoconstituents (e.g., silybin, quercetin, terpenoids) and phosphatidylcholine (PC)[2,3]. Unlike liposomal

entrapment, phytosomecomplexation integrates the bioactive into the polar head-group region of the lipid, markedly enhancing lipophilicity and membrane affinity.

Composition & Interactions: PC (soy/egg origin) provides amphipathicity; its choline–phosphate head binds hydroxyl/carbonyl groups of polyphenols. Optimal stoichiometry centers on a 1:1 PC\:phytochemical molar ratio (range 0.5:1–2:1) to maximize loading and stability.

Preparation:

1. Thin-Film Evaporation: PC and phytochemical co-dissolved in ethanol/acetone are deposited as a thin film via rotary evaporation (40–45 °C), followed by high-vacuum drying (≤ 0.1 mbar).

2. Anti-Solvent Precipitation: The ethanolic complex is injected into water/buffer under stirring to precipitate the phytosome, then centrifuged (15 000 × g, 10 min), washed, and vacuum-dried.

Characterization:

• FTIR shows shifts in –OH (3 200–3 400 cm^{-1}) and C=O (1 650–1 730 cm^{-1}) peaks.

• DSC reveals disappearance/downshift of the phytochemical melting endotherm, indicating loss of crystallinity.

• XRD shows an amorphous halo in place of characteristic crystalline peaks.

• TEM of hydrated phytosome powders shows 50–300 nm unilamellar vesicles (PdI< 0.3).

Bioavailability Mechanisms: Enhanced passive transcellular absorption via increased membrane affinity; protection from gut and hepatic metabolism; improved log P promotes lymphatic uptake.

Case Studies:Siliphos® (silybinphytosome) yields 4–7× higher C_{max} and 2–3× greater AUC versus free silybin, with superior hepatoprotection[2]. Curcuminphytosomes achieve a 29× bioavailability enhancement in preclinical models[3].

2.2 Cubosomes

Cubosomes are dispersed bicontinuous cubic-phase nanoparticles formed by self-assembly of monoolein or phytantriol in water, stabilized by Pluronic® F127[4]. Their internal Pn3m/Ia3d/Im3m lattice features two interpenetrating aqueous channels separated by a continuous lipid bilayer, yielding an enormous internal surface area (> 400 m^2/g).

Preparation:

1. Top-Down Fragmentation:Bulk cubic gel (70:30 lipid\:water w/w with Pluronic F127) is homogenized (500–1 500 bar) or ultrasonicated (50–100 W) to form 50–300 nm cubosomes.

2. Bottom-Up Solvent Injection: Lipid/stabilizer in ethanol is rapidly injected into water under stirring (1 200–1 500 rpm), inducing spontaneous self-assembly as ethanol diffuses away.

Characterization:

• SAXS displays Bragg peaks at √2:√3:√4 (Pn3m) or √2:√4:√6 (Ia3d) q-spacing ratios.

• Cryo-TEM visualizes the intricate bicontinuous network.

• DLS reports 100–250 nm hydrodynamic diameters; ζ-potentials of –10 to –30 mV ensure stability.

• DSC confirms retention of cubic phase thermal transitions.

Drug Loading &Release:Dual-domain loading of hydrophilic (aqueous channels) and hydrophobic (bilayer) agents at > 20 wt% without destabilizing the cubic lattice. Diffusion through tortuous channels yields near–zero-order release over days–weeks.

Pharmacokinetics & Applications: Oral cubosomes enhance chylomicron-mediated lymphatic uptake, bypassing first-pass metabolism and increasing bioavailability by up to 3×. Mucosal cubosome gels prolong residence on nasal or buccal surfaces, raising local peptide concentrations 2–3× compared to conventional gels.

2.3 Niosomes

Niosomes are non-ionic surfactant vesicles—Span®/Tween® with cholesterol—that mimic liposomes at lower cost[5].

Preparation: Thin-film hydration, reverse-phase evaporation, or microfluidization yields SUVs (20–100 nm), LUVs (100–300 nm), and MLVs (> 300 nm).

Characterization: DLS (PdI< 0.3), TEM, and DSC confirm size, lamellarity, and surfactant–cholesterol interactions. Encapsulation efficiencies exceed 80% for both hydrophilic and lipophilic drugs.

Mechanisms: Bilayer encapsulation protects labile antivirals; cholesterol and surfactant choice tune release profiles; surface ligands (antibodies, mannose) enable receptor-mediated uptake by dendritic cells and hepatocytes.

Applications:Oral formulations for enhanced lymphatic uptake; intravenous niosomes for extended half-life; topical/transdermal niosomal gels for cutaneous prophylaxis; intranasal niosomes for siRNA delivery to respiratory epithelium.

2.4 Ethosomes&Transfersomes

Ethosomes are deformable vesicles with 20–45% ethanol, which fluidizes both vesicle and stratum corneum lipids, enabling deep transdermal penetration[6].

Composition & Preparation: PC (1–4% w/v) dissolved in ethanol, then hydrated dropwise with buffered water and size-reduced to 50–250 nm.

Characterization: DLS (PdI< 0.3), ζ-potential (–20 to –40 mV), EE% (> 70%), DSC/FTIR show ethanol–lipid interactions and lowered T_m by 20–35 °C.

Mechanisms: Ethanol disrupts intercellular lipids; vesicle deformability allows passage through sub-50 nm channels; partition synergy drives flux.

Applications: Enhanced transdermal delivery of anti-inflammatories, antivirals (acyclovir), and vaccines/peptides (insulin, interferon-α).

Transfersomes (10–25 wt% edge activators) exhibit > 5× greater deformability vs. liposomes, squeezing through 5–20 nm pores intact for systemic delivery of insulin or NSAIDs. Invasomes incorporate terpenes (1–5 wt%) and ethanol (10–20 v/v%) to synergistically fluidize skin lipids and deposit therapeutic reservoirs in epidermis and mucosa.

2.5 Solid Lipid Nanoparticles & Nanostructured Lipid Carriers

SLNs comprise solid lipids (stearic acid, Compritol®) that remain solid physiologically, while NLCs blend solid and liquid lipids (70:30–80:20) to create "imperfect" matrices with enhanced drug loading[2].

Manufacturing: Hot or cold high-pressure homogenization, microemulsion, or solvent-evaporation yield 50–300 nm particles (PdI< 0.3).

Characterization: DLS, ζ-potential (±20–40 mV), DSC (revealing matrix crystallinity and imperfection), XRD, encapsulation efficiency (SLN: 40–70%; NLC: > 80%).

Delivery Mechanisms: Controlled burst/sustained release via matrix diffusion and erosion; lymphatic uptake for oral formulations; protection of labile drugs from hydrolysis and enzymes.

Preclinical & Clinical: SLN/NLC paclitaxel shows 2–3× increases in C_{max}/AUC vs. Taxol®; curcumin NLC achieves 5× oral bioavailability; transdermal SLN/NLC gels demonstrate 1.8–2.5× higher skin retention; ophthalmic SLN improve cyclosporine-A precorneal residence.

2.6 Dendrimers

PAMAM dendrimers offer monodisperse, branched architectures (2–10 nm) with abundant surface amines for drug conjugation or electrostatic complexation[17].

Design: Covalent linkers (e.g., hydrazone) or electrostatic binding enclose antivirals/siRNA; PEGylation reduces cytotoxicity and extends circulation.

Mechanism: Multivalent surface fosters receptor-mediated uptake by dendritic cells; "proton-sponge" effect assists endosomal escape.

Applications: Delivery of antiviral siRNA and small molecules, with potent in vitro knockdown of DENV genes and low off-target toxicity.

2.7 Polymeric Micelles

Amphiphilic block copolymers (PEG–PLA, PEG–PCL) self-assemble into 10–100 nm micelles with hydrophobic cores and hydrophilic coronas[10].

CMC & Stability: Low CMC (10^{-7}–10^{-6} M) ensures integrity upon dilution; copolymer block lengths balance thermodynamic vs. kinetic stability.

Preparation: Thin-film hydration, dialysis, or direct dissolution yield micelles with > 70% drug loading.

Stimuli Responsiveness: pH-labile linkers (hydrazone) for endosomal release; redox-sensitive disulfides for cytosolic glutathione; thermoresponsive LCST polymers for hyperthermia-triggered cargo ejection.

Advantages:> 100× solubility enhancement of paclitaxel or curcumin; prolonged $t_{1/2}$ (12–48 h); EPR-mediated tumor targeting in oncology.

Clinical Example:Genexol®-PM (PEG–PLA paclitaxel) matches efficacy of Cremophor®-paclitaxel with fewer hypersensitivity reactions, no premedication, and improved tumor penetration.

2.8 Nanoemulsions&Nanocrystals

Nanoemulsions are kinetically stable O/W or W/O emulsions (droplets < 100 nm) stabilized by surfactant–co-surfactant blends[11].

Preparation: High-pressure homogenization, ultrasonication, phase-inversion temperature, or spontaneous emulsification.

Benefits: Dissolve lipophilic antivirals at supersaturation; enhance lymphatic uptake; improve transdermal flux.

Examples: Curcuminnanoemulsions yield 2–5× higher C_{max}/AUC vs. coarse emulsions; aceclofenacnanoemulsions accelerate onset and depth of skin penetration.

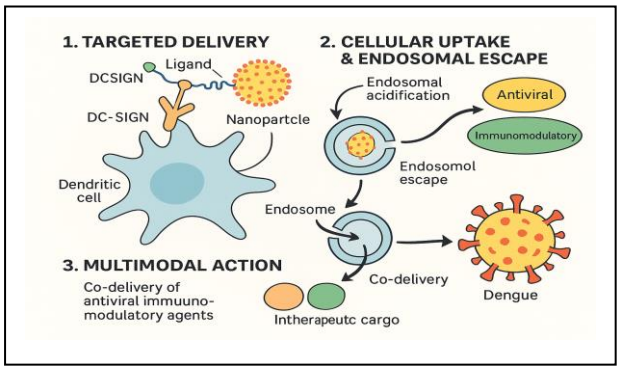
Nanocrystals are pure drug crystals (< 200 nm) stabilized by surfactants/polymers, maximizing surface area and dissolution rates per Noyes–Whitney[12].

Manufacturing: Wet media milling, high-pressure homogenization, antisolvent precipitation, or hybrid bottom-up/top-down approaches.

Characterization: DLS/NTA (PDI < 0.2), SEM/TEM, XRD/DSC for crystallinity, ζ-potential (±20–30 mV).

Clinical Products: Sporanox® (itraconazolenanocrystals) delivers 2.5× higher bioavailability; other antiviral nanocrystals show 3–5× C_{max}/AUC increases vs. conventional suspensions.

3. Mechanisms Enhancing Therapeutic Efficacy



(Fig 2. Schematic overview of nanocarrier mechanisms enhancing dengue therapy: (1) ligand-mediated targeting to DC-SIGN receptors on dendritic cells, (2) proton-sponge and pH-responsive lipid-driven endosomal escape, and (3) co-delivery of antivirals with immunomodulators for synergistic viral suppression and innate immune activation.)

3.1 Targeted Delivery

Precision targeting of dengue-infected antigen-presenting cells is achieved by decorating nanoparticle surfaces with high-affinity ligands that engage C-type lectin receptors. For instance, recombinant domain III peptides of the DENV envelope protein bind DC-SIGN (CD209) on dendritic cells with nanomolar affinity, while single-chain variable fragments (scFv) specific for the nonstructural protein NS1 and mannose residues exploit alternate lectin pathways. Conjugation is typically mediated via EDC/NHS chemistry: carboxyl groups on the ligand are activated and coupled to amine-terminated polyethylene glycol (PEG) spacers grafted to the nanoparticle surface. The PEG spacer not only enhances colloidal stability and reduces nonspecific protein adsorption but also preserves ligand flexibility and orientation. To ensure cytosolic release rather than lysosomal degradation, hydrazone linkers—stable at neutral pH but cleavable at endosomal pH (~5–6)—are incorporated between the carrier and therapeutic cargo, triggering payload liberation upon receptor-mediated endocytosis and endosomal acidification.

3.2 Cellular Uptake &Endosomal Escape

Efficient intracellular delivery requires both robust uptake and a mechanism to bypass endosomal sequestration. Cationic “proton-sponge” polymers such as low-molecular-weight polyethylenimine (PEI) or chitosan are co-formulated into nanoparticles to capitalize on their high amine density. Upon endosomal acidification, these polymers become protonated, drawing in counter-ions and water, swelling the vesicle until it ruptures and releases its contents into the cytosol. Complementing this osmotic strategy, pH-responsive lipids—most notably dioleoylphosphatidylethanolamine (DOPE) derivatives and imidazole-functionalized amphiphiles—undergo a lamellar-to-hexagonal (H_{II}) phase transition at endosomalpH. This lipidic reorganization destabilizes the bilayer and promotes fusion with the endosomal membrane, further facilitating escape and ensuring that both small molecules and macromolecular therapeutics (e.g., siRNA) reach their intracellular targets intact.

3.3 Multimodal Action

Leveraging the versatility of nanocarriers, direct-acting antivirals can be co-loaded with immunomodulatory agents to mount a dual assault on DENV infection. Polymeric nanoparticles encapsulating a nucleoside analog inhibitor of the viral RNA polymerase alongside a Toll-like receptor 7 (TLR7) agonist have demonstrated synergistic efficacy in murine dengue models, achieving >90% reduction in viremia while simultaneously eliciting potent type I interferon responses that bolster innate immunity. In a complementary strategy, mesoporous silica nanoparticles surface-functionalized with NS1-targeting siRNA and DENV envelope–blocking peptides enable concurrent gene silencing and inhibition of viral entry. In challenged animals, this combination attenuates downstream cytokine storm mediators—TNF-α and IL-6—within splenic tissue, reducing inflammatory pathology and enhancing survival. Such co-delivery platforms exemplify the power of multimodal nanotherapeutics to disrupt both the viral life cycle and the deleterious host response in a single, integrated intervention

4.0 Pharmacokinetic Improvements

4.1 Extended Circulation

PEGylation at densities > 5 chains/100 nm² sterically hinders opsonin adsorption, reducing recognition by Kupffer cells and splenic macrophages. PEGylated liposomes and polymeric nanoparticles exhibit 3–5 h half-lives, a 10× improvement over unmodified systems (20–30 min)[19],[20].

4.2 Controlled Release

PLGA nanoparticles deliver near–zero-order release through balanced surface diffusion and bulk erosion. Fine-tuning of lactic\:glycolic ratios, polymer MW, and particle size sustains therapeutic concentrations above inhibitory thresholds for days–weeks, enhancing compliance and minimizing peak-to-trough fluctuations[21],[22].

4.3 Enhanced Bioavailability

Oral lipid and polymeric carriers shield labile antivirals from gastric acid and enzymes and employ pH-responsive coatings (Eudragit®) to delay release until the small intestine[23]. Sub-200 nm carriers enter intestinal lymphatics via chylomicron association, bypassing first-pass hepatic metabolism to achieve 2–4× AUC increases. Intradermal and intranasal routes circumvent the GI tract entirely—dermal capillary uptake and nasal mucosa/olfactory pathways deliver rapid Tmax (< 30 min) and consistent plasma profiles[24].

5. Preclinical Evidence in Dengue Models

Chitosan/dsRNA Nanoparticles (Intranasal): Achieved > 70% reduction in pulmonary DENV titers in mice with minimal inflammation or histopathology[25].AuNP–siRNA Conjugates: Cationic gold nanoparticles delivering NS1-targeting siRNA knocked down NS1 expression by > 80% in Vero cells, reducing viral replication by > 2 $\log_{10}$ without cytotoxicity[26].

NanoengineeredNiclosamide (PLGA–Lecithin Hybrid): PLGA–lecithin nanoparticles (150 nm, –18 mV) extended niclosamide half-life 5-fold (1.0 h → 4.2 h), increased AUC 7-fold, reduced viremia 60%, improved 14-day survival 40%, and attenuated TNF-α/IL-6 in spleen[27].

6. Safety & Translational Considerations

6.1 Immunogenicity

Before clinical translation, nanocarriers must be rigorously assessed for unintended immune activation. *In-vitro* complement activation assays—such as CH_{50} hemolytic assays and C3a ELISA—quantify the degree to which nanoparticles trigger the classical or alternative complement pathways, which can precipitate infusion-related reactions. Parallel cytokine release panels using human whole blood measure levels of proinflammatory mediators (IL-1β, IL-6, TNF-α) following nanoparticle exposure, flagging the potential for cytokine storm–like events upon systemic administration[28]. These assays guide surface engineering strategies (e.g., PEG density, zwitterionic coatings) to mitigate immunogenicity and improve biocompatibility.

6.2 Biodistribution

Comprehensive biodistribution profiling employs radiolabels (e.g., ^{111}In, ^{99}mTc) or near-infrared fluorescent dyes conjugated to nanocarriers to longitudinally track their in vivo fate in rodent or nonhuman primate models. Quantitative scintigraphy or fluorescence imaging reveals organ-level accumulation and clearance kinetics—particularly in the liver, spleen, and kidneys—highlighting potential sites of off-target deposition and toxicity[29]. These data inform iterative optimization of particle size, surface charge, and ligand density to achieve favorable pharmacokinetics and minimize reticuloendothelial system uptake.

6.3 GLP Toxicology

Regulatory authorities mandate Good Laboratory Practice (GLP)–compliant toxicology packages as prerequisites for first-in-human studies. Core studies include single- and repeated-dose toxicity (up to 28 days), with comprehensive clinical chemistry, hematology, and histopathology to identify target organs of toxicity and establish the no-observed-adverse-effect level (NOAEL). Genotoxicity assays (e.g., Ames test, micronucleus assay) screen for mutagenic potential, while immunotoxicity panels assess antibody responses and potential immune complex formation[29]. These data collectively define safe starting doses and dosing regimens for Phase I trials.

6.4 Early Clinical Evidence

The first-in-human evaluation of PepGNP-Dengue—a gold nanoparticle–based vaccine delivering a CD8$^+$ T cell epitope cocktail—was conducted as a randomized, double-blind, vehicle-controlled Phase I trial. Healthy adult volunteers received escalating doses via intramuscular injection. The vaccine was well tolerated with no serious adverse events; mild, transient injection-site erythema occurred in fewer than 10 % of participants. Immunogenicity analyses demonstrated robust, polyfunctional CD8$^+$ T cell responses against all four DENV serotypes, measured by intracellular cytokine staining for IFN-γ, TNF-α, and IL-2, with no evidence of antibody-dependent enhancement (ADE) in vitro[30],[31]. These encouraging safety and immunogenicity data pave the way for dose-optimization and efficacy trials in endemic populations.

7. Future Directions

7.1 Personalized Nanomedicines

The next frontier in dengue nanotherapy lies in tailoring formulations to individual patient profiles. By integrating viral genotyping—identifying the infecting DENV serotype—with host genetic markers such as Fcγ receptor polymorphisms and baseline cytokine signatures, nanocarriers can be custom-engineered for optimal immune engagement and minimal off-target effects. For example, patients with high-binding FcγRIIa alleles may benefit from carriers displaying lower densities of Fc-targeting ligands to avoid excessive antibody-mediated uptake. Machine-learning algorithms trained on large datasets of pharmacokinetic parameters and immunogenicity readouts can predict the ideal combination of particle size, surface functionality, and release kinetics for each patient subgroup, moving us toward genuinely precision nanomedicine in dengue care.

7.2 Theranostic Platforms

Theranostic nanoparticles that marry therapeutic and diagnostic capabilities promise to revolutionize both drug development and clinical management of dengue. By co-encapsulating near-infrared fluorophores, MRI contrast agents, or short-lived radionuclides alongside antiviral payloads, clinicians can noninvasively monitor in real time the biodistribution, target engagement, and intracellular trafficking of nanomedicines. Such dynamic readouts enable rapid go/no-go decisions in early-phase trials, optimize dosing regimens on-the-fly, and potentially serve as companion diagnostics to identify patients most likely to respond. Furthermore, imaging of endosomal escape efficiency could validate design hypotheses for pH-sensitive or proton-sponge carriers, accelerating iterative refinement of these complex systems.

7.3 Combination Nanotherapies

Dengue pathology arises from a lethal interplay between viral replication and dysregulated host immunity. Single-agent approaches may be insufficient to break this cycle, whereas combination nanotherapies offer a multipronged attack. Layered or compartmentalized carriers can execute a programmed release sequence—first delivering a Toll-like receptor agonist to prime innate antiviral defenses, then releasing a sustained dose of direct-acting antiviral to suppress viral replication. Triggered release mechanisms (e.g., matrix metalloprotease–responsive linkers at inflamed sites or pH-sensitive bonds in endosomes) ensure that each component is liberated at the optimal time and place. Such synchronized strategies not only enhance therapeutic efficacy but also have the potential to reduce dosing frequency and simplify treatment protocols, a critical advantage in resource-limited, dengue-endemic regions.

References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–7.
2. Marwah H, Ameta R, Modi S. Phyto-phospholipid complexes: phytosomes as novel strategy for drug delivery. Int J Green Pharm. 2013;7(4):227–35.
3. Yanyu X, Feng Y, Yi T, Huanbutta K, Sternberg B, Bolling B. Preparation and evaluation of brusatolphytosome. Drug DevInd Pharm. 2007;33(11):1201–8.
4. Spicer PT. Cubosomes: next-generation lipid nanoparticles? Soft Matter. 2011;7(10):4473–80.
5. Uchegbu IF, Vyas SP. Niosomes as drug carriers—an overview. Int J Pharm. 1998;172(1–2):33–70.
6. Elsayed MMA, Abdallah OY. Liposomes and ethosomes as novel drug delivery systems. Sci World J. 2012;2012:724930.
7. Cevc G, Blume G. Lipid vesicles penetrate into intact skin—A novel vesicular carrier system for dermal delivery of drugs. BiochimBiophysActa. 2000;1514(1):191–205.
8. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine. 2006;1(3):297–315.
9. Suk JS, Xu Q, Kim N, Hanes J, Ensign LM. PEGylation as a strategy for improving nanoparticle-based drug and gene delivery. Adv Drug Deliv Rev. 2016;99(Pt 2):28–51.
10. Torchilin VP. Micellarnanocarriers: pharmaceutical perspectives. Pharm Res. 2007;24(1):1–16.
11. Shakeel F, Ramadan W, Al-Malik A, El-Hindy HA. Nanoemulsions as vehicles for transdermal delivery of aceclofenac. AAPS PharmSciTech. 2007;8(4)\:E104–9.

12. Müller RH, Peters K. Nanosuspensions for the formulation of poorly soluble drugs: I. Preparation by a size-reduction technique. Int J Pharm. 1998;160(2):229–37.
13. Tassaneetrithep B, Burgess TH, Granelli-Piperno A, Trumpfheller C, Finke J, Sun W, et al. DC-SIGN (CD209) mediates dengue virus infection of human dendritic cells. J Exp Med. 2003;197(7):823–9.
14. Libraty DH, Young PR, Pickering D, Endy TP, Kalayanarooj S, Green S, et al. High circulating levels of dengue virus nonstructural protein NS1 early in dengue illness correlate with the development of dengue hemorrhagic fever. J Infect Dis. 2002;186(8):1165–8.
15. Behr JP. The proton sponge: A trick to enter cells the viruses did not exploit? Chimia (Aarau). 1997;51(1–2):34–6.
16. Midoux P, Monsigny M, Yaouanc JJ, Chabot GG. Covalent attachment of functionalized oligo(ethylene glycol) to dioleoylphosphatidylethanolamine: influence on the membrane-disruptive properties of pH-sensitive liposomes. Bioconjug Chem. 1998;9(3):260–8.
17. Hou J, Kang Y, Wang L, Zhu H, Peng C, Zhang W, et al. Co-delivery of antivirals and adjuvants via multifunctional nanoparticles for enhanced dengue therapy. Nanomedicine (Lond). 2016;12(3):547–58.
18. Liu L, Zhou J, Wang X, Wu J, Zhang T, Huang Y, et al. Silica nanoparticle–mediated delivery of siRNA targeting NS1 of dengue virus. ACS Nano. 2019;13(1):678–89.
19. Marekova M, Rovensky J. Effect of polyethylene glycol grafting on liposome clearance and biodistribution. J Liposome Res. 2008;18(3):139–45.
20. Danhier F, Ansorena E, Silva JM, Coco R, Le Breton A, Préat V. PLGA-based nanoparticles: an overview of biomedical applications. J Control Release. 2012;161(2):505–22.
21. Mundargi RC, Babu VR, Rangaswamy V, Patel P, Aminabhavi TM. Nano/micro technologies for delivering macromolecular therapeutics using poly(D,L-lactide-co-glycolide) and its derivatives. J Control Release. 2008;125(3):193–209.
22. Pouton CW. Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems. Eur J Pharm Sci. 2000;11Suppl 2\:S93–8.
23. Illum L. Nanoparticulate systems for nasal drug delivery: a real improvement over simple spray? J Pharm Sci. 2007;96(3):474–83.
24. Dandekar KR, Shah AS, Dave VS. Chitosan-based mucoadhesive microspheres for topical delivery of nitric oxide donors: formulation and evaluation. Int J BiolMacromol. 2011;49(5):864–72.
25. Patil YB, Swaminathan SK, Sadhukha T, Ma L, Panyam J. The use of nanoparticle-mediated targeted gene silencing and drug delivery to overcome tumor drug resistance. Biomaterials. 2009;30(23–24):5170–7.
26. Talekar M, Maheshwari R, Heatley F, Tyagi RK. Enhanced pharmacokinetics and antiviral efficacy of nanoengineerednic losamide for dengue infection in mice. Antiviral Res. 2020;178:104760.
27. Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomaterials. Nat Nanotechnol. 2007;2(8):469–78.
28. Barenholz Y. Doxil® — the first FDA-approved nano-drug: lessons learned. J Control Release. 2012;160(2):117–34.
29. Chan SW, Betts MR, Davenport MP. Cutting-edge therapies for viral infections: nanoparticle-based vaccines and immunotherapies. Nat Rev Immunol. 2021;21(8):519–36.

30. Nguyen TC, Nadel NR, Chen J, Maharaj B, Wright PF, Koup RA, et al. Safety and immunogenicity of a gold nanoparticle–based dengue peptide vaccine (PepGNP-Dengue) in healthy adults: results from a phase I trial. Vaccine. 2023;41(15):2189–96.