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Short Communication

Dendrosomes as Emerging Multifunctional Nanocarriers for Targeted Drug Delivery: Opportunities, Challenges, and Future Perspectives a Short Communication

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ABSTRACT

Dendrosomes are supramolecular, vesicular nanocarriers formed by encapsulating dendrimers, or dendrimer complexes with a therapeutic payload, within a liposomal lipid shell. First described by Sarbolouki and co-workers as a non-viral vector for gene transfer, the dendrosome concept has since expanded into a versatile platform for delivering small-molecule drugs, nucleic acids, and natural bioactive compounds. By combining the internal cavities and surface-functionalizable branching of dendrimers with the biocompatibility, amphiphilicity, and membrane-mimetic character of liposomes, dendrosomes mitigate the cationic-charge-associated cytotoxicity of dendrimers while improving the payload-carrying capacity and stability of conventional liposomes. This short communication summarizes the structural basis, synthesis strategies, and representative therapeutic applications of dendrosomes, with particular emphasis on dendrosomal nanocurcumin as the most extensively studied system, and on dendrosome-mediated gene and siRNA delivery. Key translational challenges, including batch-to-batch reproducibility, scale-up, long-term biosafety, and regulatory characterization, are discussed alongside emerging opportunities in ligand-mediated active targeting, stimuli-responsive release, and combination therapy.

INTRODUCTION

The clinical translation of many potent therapeutic agents, particularly hydrophobic small molecules, peptides, and nucleic acids, is limited by poor aqueous solubility, rapid systemic clearance, off-target toxicity, and inefficient intracellular

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delivery [1,2]. Nanocarrier-based drug delivery systems have therefore been developed to improve pharmacokinetics, protect labile cargo, and, where possible, direct therapeutic agents preferentially toward diseased tissue [1,2]. Among the nanocarrier families explored for this purpose, dendrimers are hyperbranched, monodisperse macromolecules with a well-defined core-shell architecture, an interior capable of hosting guest molecules, and a densely functionalizable peripheral surface [1]. These properties make dendrimers attractive drug and gene carriers, but higher-generation cationic dendrimers, most notably polyamidoamine (PAMAM), can produce concentration- and generation-dependent membrane disruption and haemolytic toxicity that constrains their systemic use [1,3].

To address this limitation while retaining the structural advantages of dendrimers, Sarbolouki and colleagues introduced the term "dendrosome" in 2000 to describe a family of synthetic, hyperbranched, spherical, lipid-based vehicles for direct gene delivery into cultured cells and animal models [3]. Subsequent work refined the concept: dendrosomes are now generally understood as liposomal vesicles in which a dendrimer, or a dendrimer complexed with a nucleic acid or drug (dendriplex), is entrapped within or associated with a phospholipid bilayer shell [4]. This hybrid design shields the charged dendrimer surface from direct contact with biological membranes, lowering cytotoxicity and haemolysis while improving payload protection, circulation stability, and cellular uptake relative to either component used alone [3,4]. Given the accumulating evidence for their multifunctionality, this short communication provides a focused overview of dendrosome architecture, representative applications in cancer therapy and gene delivery, and the principal opportunities and barriers that will determine their clinical trajectory.

Table 1. Emergence and evolution of dendrosomes as nanocarriers.

Year	Milestone / Development	Reference
2000	Term "dendrosome" coined; first-generation lipid-enveloped dendritic vehicles reported for direct gene transfection in cell culture and animal models.	Sarbolouki et al. [3]
2010	Dendrosome-encapsulated dendriplexes used to deliver siRNA against HPV E6/E7 oncogenes in cervical cancer cells, demonstrating reduced dendrimer-associated toxicity.	Dutta et al. [13]
2012	Dendrosomal curcumin formulation shown to suppress cancer cell proliferation in vitro and in vivo, establishing the platform for natural-compound delivery.	Babaei et al. [6]
2013	Conceptual framing of dendrosomes alongside vesosomes as modular, multicompartment lipid-based drug and gene delivery carriers.	Paleos et al. [2]
2015	Comprehensive formulation review describing amphiphilic oleic acid-PEG dendrosomes for curcumin encapsulation and improved bioavailability.	Tahmasebi Birgani et al. [5]
2016-2018	Mechanistic expansion: dendrosomal nanocurcumin combined with p53 re-expression, miRNA/epigenetic modulation, and	Keshavarz et al. [10]; Chamani et al. [12]; Mahjoub et al.

Year	Milestone / Development	Reference
	chemotherapeutics (doxorubicin) in breast, liver, and brain cancer models.	[11]; Baghi et al. [9]
2024	Continued mechanistic refinement showing dendrosomal curcumin-induced mitochondrial apoptosis and cell-cycle arrest in breast cancer cells.	Abbasi et al. [8]

2. *Structural* Architecture and Synthesis

Structurally, dendrosomes occupy an intermediate position between liposomes and dendrimers, combining an outer lipid bilayer, typically composed of phospholipids such as egg phosphatidylcholine or dioleoylphosphatidylethanolamine together with cholesterol, with an inner dendrimeric or dendriplex core [2,4]. Two broad architectural variants have been reported. In the first, exemplified by early gene-delivery dendrosomes, an amphiphilic dendron built from esterified oleic acid and polyethylene glycol chains self-assembles directly into a spherical, micellar, or polymersome-like structure capable of encapsulating hydrophobic drugs such as curcumin [5]. In the second, cationic dendrimer-nucleic acid dendriplexes are pre-formed and subsequently loaded into the aqueous core of conventional liposomes, yielding a lipid-enveloped dendriplex particle [4,6]. Both approaches converge on the same functional outcome: a lipid interface that improves biocompatibility and controls release, wrapped around a branched macromolecular core that provides high payload density and multivalent surface chemistry [2,4].

Preparation methods draw on established liposome technology, including thin-film hydration, solvent injection, and extrusion or sonication for size reduction, followed by characterization of particle size, zeta potential, polydispersity, and encapsulation efficiency [4,6]. Because the dendrimer core and lipid shell can each be independently modified, dendrosomes are inherently multifunctional platforms: the dendrimer periphery can be conjugated with targeting ligands, imaging tags, or stimuli-responsive linkers, while the lipid shell can be PEGylated to extend circulation time or functionalized with antibodies, peptides, or aptamers for active targeting [2,4].

Table 2. Principal structural components of a dendrosome and their functional roles.

Structural Component	Composition / Description	Functional Role
Outer lipid bilayer shell	Phospholipids (e.g., egg phosphatidylcholine, DOPE) combined with cholesterol, arranged as a liposome-like membrane.	Confers biocompatibility and membrane-mimetic behavior; shields the charged dendrimer core; modulates release rate and reduces haemolytic toxicity.
Inner dendrimer / dendriplex core	Hyperbranched macromolecule (e.g., PAMAM) alone, or complexed with a drug, DNA, or siRNA payload.	Provides high payload-carrying capacity, multivalent internal cavities, and condensation of nucleic acid cargo.

Structural Component	Composition / Description	Functional Role
Aqueous interlayer	Hydrated space between the dendrimer core and the surrounding lipid bilayer.	Houses the dendriplex; buffers direct contact between core and membrane; helps protect nucleic acid cargo from enzymatic degradation.
Dendrimer peripheral groups	Terminal amine, hydroxyl, or carboxyl functional groups on the dendrimer branches.	Serve as conjugation sites for targeting ligands, fluorescent or imaging tags, and stimuli-responsive linkers.
Lipid surface modifications (optional)	PEG chains, antibodies, peptides, or aptamers grafted onto the outer lipid surface.	Extend circulation half-life (stealth effect) and enable active, receptor-mediated targeting of diseased tissue.

DOPE, dioleoylphosphatidylethanolamine; PAMAM, polyamidoamine; PEG, polyethylene glycol.

Table 3. Comparative structural and functional features of dendrimers, liposomes, and dendrosomes.

Feature	Dendrimers	Liposomes	Dendrosomes
Core architecture	Solid hyperbranched macromolecule	Hollow aqueous core within a lipid bilayer	Dendrimer or dendriplex core enclosed within a lipid bilayer
Payload capacity	High (internal cavities and surface conjugation)	Moderate (aqueous core and bilayer)	High (dendrimer core plus bilayer/interlayer)
Surface functionalization	Extensive, via peripheral groups	Moderate, via lipid head-group chemistry	Extensive, on both dendrimer periphery and lipid surface
Cytotoxicity / haemolysis	Generation-dependent, can be significant for cationic types	Generally low	Reduced relative to unshielded cationic dendrimers
Structural stability	High (covalent branching)	Moderate (susceptible to fusion/leakage)	Enhanced by combining dendrimer rigidity with lipid flexibility
Typical application focus	Small-molecule and nucleic acid carriers	Small-molecule, protein, and nucleic acid carriers	Nucleic acid, siRNA, and hydrophobic natural-compound delivery

3. Multifunctionality in Drug, Gene, and Bioactive Delivery

3.1 Anticancer applications: dendrosomal nanocurcumin

The most extensively investigated dendrosomal system in the literature is dendrosomal nanocurcumin (DNC), developed to overcome the very low aqueous solubility, rapid metabolism, and poor bioavailability that otherwise limit the anticancer potential of curcumin, a polyphenolic compound derived from Curcuma longa [5]. Encapsulation within a dendrosome markedly increases curcumin's apparent solubility and

cellular uptake relative to the free compound [5]. DNC has demonstrated antiproliferative and pro-apoptotic activity across a range of malignant cell lines and animal tumor models, including breast, bladder, colon, hepatocellular, and glioblastoma cancers, generally acting through modulation of apoptosis-related genes and proteins such as Bax, Bcl-2, p53, and downstream survival pathways [5,7]. In breast cancer models, DNC has been shown to induce mitochondrial apoptosis and cell-cycle arrest at the SubG1 phase, accompanied by upregulation of pro-apoptotic factors (Bax, Noxa, PUMA, p21) and downregulation of anti-apoptotic and proliferative markers (Bcl-2, EZH2, Lnc-DANCR) [8]. DNC also acts synergistically with both exogenous tumor-suppressor gene expression and conventional chemotherapeutics: co-treatment with re-introduced p53 potentiates apoptosis in breast cancer and glioblastoma cells [9,10], while combination with doxorubicin enhances anticancer activity in metastatic breast cancer cells partly through modulation of the CXCR4/NF-κB/Smoothened signaling network [11]. In hepatocellular carcinoma cells, DNC treatment has additionally been linked to altered expression of the miR-34 family and DNA methyltransferases, suggesting an epigenetic dimension to its activity [12].

3.2 Gene and siRNA delivery

Beyond small-molecule delivery, dendrosomes retain strong utility as nucleic acid carriers, the application for which the platform was originally conceived [3]. Encapsulating a pre-formed dendrimer-siRNA dendriplex within a lipid shell mitigates the cytotoxicity associated with the high dendrimer generations required for effective nucleic acid condensation, while preserving gene-silencing performance. In a representative study, dendrosomal delivery of siRNA targeting the human papillomavirus E6 and E7 oncogenes achieved substantial knockdown in cervical cancer cells, with the lipid shell masking toxicity that was otherwise observed with the naked dendriplex [13]. More broadly, dendrosome-encapsulated dendriplexes have been explored as vectors for plasmid DNA and other genetic material, offering low haemolytic toxicity, favorable transfection efficiency, and good in vivo tolerance relative to unshielded cationic dendrimers or lipoplexes [4,6]. Multicompartment variants, in which liposomes encapsulate either smaller liposomes (vesosomes) or dendrimers (dendrosomes), have further been proposed as universal modular platforms capable of co-delivering combinations of drugs and genetic material with tunable release kinetics [4].

3.3 Vaccine and immunomodulatory applications

Dendrosomes have also been investigated as nano-sized adjuvants for genetic immunization, capitalizing on their capacity to protect entrapped nucleic acid from enzymatic degradation while promoting efficient cellular uptake by antigen-presenting cells [4,6]. Such applications extend the multifunctional scope of the platform beyond conventional chemotherapy into prophylactic and immunotherapeutic domains, although this area remains comparatively less developed than the oncology-focused literature.

4. Opportunities for Targeted Delivery

Several features position dendrosomes favorably for targeted drug delivery. First, their dual-component architecture allows independent, orthogonal functionalization of the lipid surface and the dendrimer periphery, enabling combinations of passive targeting (via PEGylation and enhanced permeability and retention in solid tumors) with active targeting (via ligand conjugation to receptors overexpressed on diseased cells) [2,4]. Second, the internal branching of the dendrimer core provides high payload capacity and the possibility of co-loading

chemically dissimilar agents, for example a hydrophobic small molecule together with a nucleic acid, supporting rational combination therapy [4,11]. Third, because both dendrimers and liposomes are chemically tunable, dendrosomes are compatible with stimuli-responsive designs, such as pH-, redox-, or enzyme-sensitive linkers, that could enable triggered release within the tumor microenvironment or endosomal compartment. Finally, relative to unshielded high-generation dendrimers, the lipid envelope of dendrosomes measurably reduces haemolytic and cytotoxic liabilities, which is an important step toward systemic administration [3,4].

5. Challenges

Despite this promise, several obstacles must be resolved before dendrosomes can progress toward clinical use. Reproducible, scalable synthesis remains a central concern: multi-step assembly of dendrimer or dendriplex cores followed by lipid encapsulation introduces batch-to-batch variability in particle size, encapsulation efficiency, and surface charge that complicates good manufacturing practice-compliant production [2,4]. Comprehensive long-term toxicological and immunogenicity data, particularly for cationic dendrimer components and for repeated dosing regimens, are still limited relative to more established nanocarrier classes such as liposomes and polymeric nanoparticles [1,3]. Physicochemical characterization is similarly demanding, since dendrosomes possess a more complex, multicompartment architecture than single-component nanocarriers, requiring orthogonal analytical methods to confirm dendrimer encapsulation, payload location, and structural integrity during storage [4]. Regulatory pathways for such hybrid, multicomponent nanomedicines are not yet well established, and in vivo pharmacokinetic and biodistribution data, especially in large-animal and human studies, remain sparse compared with the extensive in vitro literature [1,2]. Cost and complexity of production relative to simpler liposomal formulations may also limit near-term commercial adoption.

FUTURE PERSPECTIVES

Future work should prioritize standardized, scalable manufacturing protocols and harmonized characterization criteria to enable meaningful comparison across studies. Systematic in vivo pharmacokinetic, biodistribution, and chronic toxicity studies are needed to translate the substantial in vitro anticancer and gene-silencing data into credible preclinical development candidates. Incorporation of active-targeting ligands and stimuli-responsive chemistries offers a route toward more precise, tumor- or tissue-selective delivery, while co-encapsulation strategies that pair dendrosomal nanocurcumin or other natural compounds with conventional chemotherapeutics may help address multidrug resistance through synergistic, multi-pathway mechanisms [5,11]. Expanding dendrosome research beyond oncology, into gene therapy, vaccination, and inflammatory or infectious disease applications, would also help clarify the general versatility of the platform. With coordinated attention to reproducibility, safety characterization, and regulatory alignment, dendrosomes are well positioned to mature from a promising laboratory-stage nanocarrier into a clinically viable multifunctional delivery platform.

CONCLUSION

Dendrosomes combine the payload capacity and surface tunability of dendrimers with the biocompatibility and membrane-mimetic properties of liposomes, yielding a multifunctional nanocarrier platform with demonstrated activity in anticancer drug delivery, gene and siRNA

delivery, and genetic immunization. Dendrosomal nanocurcumin, in particular, illustrates how this hybrid design can substantially improve the solubility, cellular uptake, and therapeutic efficacy of a poorly bioavailable natural compound. Realizing the full clinical potential of dendrosomes will require sustained progress in reproducible synthesis, in vivo safety and pharmacokinetic characterization, and targeted delivery engineering.

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