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Review Article

DENDRIMERS: ADVANCEMENTS IN NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Dendrimers exhibit unique physicochemical properties, such as internal cavities and surface functionality, that enhance their effectiveness as drug delivery vehicles, improving solubility and stability of therapeutics. Various dendrimer types, including dendritic polymers and hyper branched polymers, are discussed in terms of their customization for targeted drug administration. The study further evaluates the development of dual-responsive nanoparticles (PDPP@D), which demonstrate enhanced penetration in solid tumors, and explores dendron-polymer conjugates as nanosized drug delivery systems. The findings showcase dendrimers' capability to encapsulate therapeutic agents, facilitating controlled release and improved efficacy in treating diseases such as cancer and neuroinflammation. In addition, the research highlights challenges in clinical translation, including issues of cytotoxicity and immune response, while underscoring the promise of dendritic structures in advancing personalized medicine and combating drug-resistant pathogens. Overall, this study contributes to the understanding of dendrimers in biomedical applications, emphasizing their role in innovative drug delivery systems and therapeutic strategies.

Keywords: Dendrimers, Drug delivery, Nanomedicine, physicochemical properties, Targeted drug administration, Dual-responsive nanoparticles, Solid tumors, Dendron-polymer conjugates, Controlled release, cancer, Neuroinflammation, Clinical translation, Cytotoxicity, Personalized medicine, Drug-resistant pathogens

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INTRODUCTION

The term "dendrimer" is derived from the Greek word "dendron," meaning tree or branch [2]. The first "cascade" and "nonskid-chain- like" molecules with molecular cavity topologies were created and published by Buhleir and associates as early as [3]. These molecules were subsequently identified as the earliest types of dendritic polymers between 1979 and 1985. Donald A. Tomalia and his team at Dow Laboratories advanced the development of dendrimers substantially [4]. They generated what Tomalia referred to as dendrimers—polymers with a central, hollow core and tendrils that branched outward, one from another, in a precise, predictable [5]. The early history of dendrimers was influenced by these two scientific communities. More than 100 dendritic structures have been documented, including poly(propylene mine) (PPI) and poly(amidoamine) (PAMAM) [6,7]. Dendrimers are a key type of nanostructured carriers used in nanomedicine to cure illnesses. Dendrimers are versatile and adaptable, making them useful for various applications. Dendrimers are a key type of nanostructured carriers used in nanomedicine to cure illnesses. Dendrimers' structural diversity and adaptability allow for many medication and gene delivery methods. Dendrimers with a hydrophobic core and hydrophilic periphery can act as unimolecular micelles, allowing for the solubilization of hydrophobic medicines by entrapping them in an intramolecular cavity [8,9]. Non-viral gene delivery systems often utilize cationic dendrimers due to their surface charge and structural compatibility. Dendrimer surface groups can be coupled with medicines and other useful molecule [1,10].

SYNTHESIS OF DENDRIMERS

Dendrimers, unlike typical polymers, have a distinct core-shell structure with three components: A core (I), an interior, and shells. Generations consist of repeated BC units (II) and terminal functional groups (III), which form the outer shell or perimeter. Dendrimer synthesis typically requires either divergent or convergent assembly processes, which require construction components. Methodologies for BC or dendron building may differ among these major approaches. Many of these topics, including experimental approaches, have been discussed elsewhere.

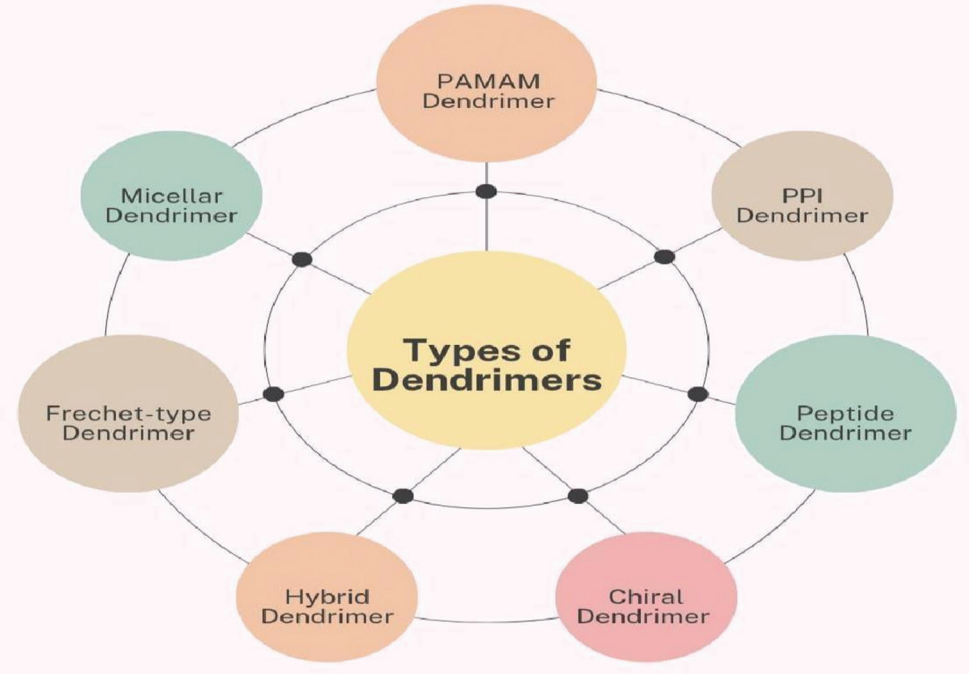
PAMAM dendrimers are synthesized using the divergent technique. In situ BC construction is done in repetitive stages around a core to get mathematical results. Core-shell structures are clearly defined. Typically, ethylenediamine (core multiplicity, Nc = 4), ammonia (NH_3) (Nc = 3), or cysteamine (Nc = 4) are utilized as cores for iterative, two-step reactions. The process involves alkylating primary amines with methyl acrylate, followed by amidation of enlarged ester groups with ethylenediamine to create primary amine terminal groups. The first reaction sequence on the exposed core results in the generation G = 0 (the core BC), where the number of dendrons anchored to the core is determined by NC. The alkylation-amidation sequence amplifies terminal groups from one to two, resulting in the formation of a BC at the dendron's anchoring point [3].

Assuming G = 1. Repeating the iterative sequence results in further shells or generations of BCs that amplify mass and terminal groups using the mathematical formulae presented. The number of terminal groups (Z) and mass amplification are determined by both the core multiplicity (Nc) and BC multiplicity (Nb) in relation to generation (G). These generation sequences can be viewed as "quantized polymerization" occurrences. Research has shown that reactive monomers, BCs, and dendrons can be assembled around atomic or molecular cores to form dendrimers based on divergent or convergent branching principles.

TYPES OF DENDRIMERS

PAMAM dendrimer

PAMAM dendrimer, first reported in 1980, is a highly branched synthetic macromolecule with a defined structure and composition. They are tunable and have a wide range of biomedical applications due to their tunable properties. The core of PAMAM dendrimer consists of exploratory data analysis (EDA), NH_3, and cystamine, with repeating



units of methacrylate and EDA added as per the generation required. The superficial branches may have different functional groups, such as amines (NH_2), hydroxyl (OH), carboxymethyl ($COOCH_3$), tert-butyloxycarbonyl (Boc), aldehyde (CHO), methyl (CH_3), or sodium carboxy (COONa). The internal cavity and peripheral functional groups can be modified for drug, gene, or imaging system encapsulation [12]. PAMAM dendrimers have a size range from 1 to 14 nm, with full-generation dendrimers with primary amine groups having a pKa of 6.85 at the surface and a tertiary amine group in the core [11,20].

PPI dendrimers

PPI dendrimer is a hydrophobic dendrimer with a high surface charge density [13]. It is synthesized using a divergent approach, with EDA as the core molecule and CN-terminated branches added through Michael addition reaction. Full-generation dendrimers can be produced using Raney nickel catalyst. PPI dendrimers have less transfection capability than other dendrimers, so different approaches are used to improve their transfection capabilities. They form stable noncovalent complexes with drugs and nucleotides, and can be modified with sugar groups to improve bioavailability [14,20].

Peptide dendrimer

Peptide dendrimers are molecules that mimic proteins and are used in nonviral vaccine delivery, immunogens, and diagnostic agents. They offer advantages such as nontoxic metabolites, economic bulk synthesis, and easy purification [15]. Peptide dendrimers have a molecular weight ranging from 2 to 100 kDa and can contain large protein structures. They are classified into three major types: grafted peptide dendrimers, which contain unnatural amino acids or organic moieties as the core, and peptide dendrimers, which contain proteins or peptides attached to them as peripheral functional groups [16,20].

Chiral dendrimer

Chiral dendrimers are structures with three parts: a core with stereogenic centers, a branch with these centers, and the attachment of chiral molecules to the surface. They are used as catalysts, in the separation of enantiomers, in sensing, and in molecular recognition [17]. Carbocosilanedendrimers, containing β cyclodextrins, are used as a chiral stationary phase in capillary electrochromatography. Other carbosilanedendrimers modified with Levo-enantiomers of cysteine and N-acetyl-L-cysteine also possess chirality. Enantiomerically pure molecules are used for synthesis, with 1,1-binaphthyl molecules being used due to their stable chiral configuration and asymmetric induction property. Chiral dendrimers based on binaphthyl core are used for selective enantiomer recognition using fluorescence, offering increased sensitivity, real-time response recording, and multiple mode detection. They can be used in high-throughput screening of chiral [18,20].

Hybrid polymer

Hybrid dendrimers combine two chemically different dendritic segments to maintain a molecular branching structure independent of others. These dendrimers, such as hydrophilic PAMAM dendrimer and hydrophobic organosilicon, have various applications and possess inherited properties of individual dendrimers. The arrangement of dendrimers, such as flexible core with rigid shell or flexible shell with rigid core, helps understand dendrimer performance. Hybrid dendrimers also have the advantage of being production-intensive [19,20].

Miceller dendrimer

Micellar types of dendrimers are fully aromatic, water-soluble hyperbranched polypropylene dendrimers that generate aromatic polymeric chains, creating a milieu resembling micellar structures, resulting in complexes with small organic molecules in water [20-22].

Gauro *et al.* investigate the use of dendritic polymers, specifically dendrimers, as carriers for topical and transdermal drug delivery. The main objectives are to overcome skin barrier properties that limit drug absorption, evaluate dendrimers' ability to improve drug solubility, penetration, and retention in skin layers, analyze interactions between dendrimers and drug molecules, and compare dendrimer-based delivery systems with conventional chemical and physical permeation enhancers. Dendrimers show promise for improving cutaneous medication delivery by increasing drug solubility and penetration. They penetrate the skin more effectively with lower-generation dendrimers due to their positive charge. They increase skin permeability for both hydrophobic and hydrophilic medicines, but perform best with lipophilic medications. Dendrimers have antibacterial, anti-inflammatory, and wound-healing characteristics, making them potentially useful as drug carriers and therapeutics [23]. Future research should focus on clinical translation, optimizing dendrimer size, charge, and surface modifications for different drug formulations, and combining dendrimers with microneedles or iontophoresis for improved systemic drug delivery through the skin [23].

Zorab *et al.* explore the composition, classification, synthesis, and applications of dendrimers, focusing on their potential for drug delivery in nanomedicine. Dendrimers' unique physicochemical properties, such as internal cavities, solubility in water, nanoscale size, and surface functionality, can be utilized for various therapeutic applications, including drug delivery and gene therapy. They are considered significant in nanomedicine due to their ability to regulate distribution, improve drug solubility and stability, and be beneficial for gene therapy, sensor generation, and drug delivery to treat neuroinflammatory disorders. The study also discusses dendrimer variants, such as dendrimers, dendrons, dendronized polymers, and hyperbranched polymers, which are used to customize the administration of medicines and other therapeutic agents. Dendrimers' intricate structure and versatility make them ideal candidates for drug delivery applications, as their multifunctional nature allows for precise encapsulation of drugs and other chemical entities, improving solubility and stability. The ability to modify dendrimer properties holds significant implications for various medical applications, including drug delivery, gene therapy, and neuroinflammation treatment [24].

Koti *et al.* developed a hyperbranched polymer-based drug delivery system to improve the bioavailability and therapeutic efficacy of hydrophobic anticancer drugs. The polymer, a dendritic polymer with hydrophobic cavities, was created using 1,6-hexanediol and a malonic acid-based A2B monomer. The polymer's structure, amorphous nature, and thermal stability were validated through various tests. The polymeric nanoparticles were created for the coencapsulation of hydrophobic medicines, and folic acid surface conjugation allowed targeted administration to A549 lung cancer cells. *In vitro* investigations showed enhanced cytotoxicity, increased drug internalization, increased reactive oxygen species production, and reduced cancer cell movement, indicating its potential to limit metastasis. The synthesized dendritic polymer is a promising candidate for cancer therapy applications due to its high biocompatibility, improved drug retention, and targeted delivery to cancer cells [25]. Mandal investigated dendron-polymer conjugates as nanosized drug delivery systems, focusing on their self-assembly, stimuli-responsive capabilities, and drug encapsulation potential. These conjugates form stable micelles sized between 10 and 200 nm, protecting drugs from enzymatic degradation while facilitating controlled release in response to pH or external stimuli [27]. Notably, RGD-modified nanoparticles enhance drug accumulation in tumors, with dendritic micelles achieving a drug loading capacity of up to 95% for doxorubicin (DOX). The study shows that at pH 5.0, 39% of the loaded drug is released, while only 20% is released at pH 7.4 over 96 h [27]. *In vivo* studies demonstrated that these micelles were 1.5 times more effective at suppressing tumor growth compared to free DOX, with minimal toxicity and clearance from the injection site within 30 h. These conjugates enhance drug solubility, stability, and controlled release, positioning them as promising platforms for drug delivery. Future challenges include optimizing large-scale synthesis and *in vivo* performance for clinical applications [27].

Two types of nanocarriers loaded with GEM were developed, one using covalent conjugation and the other by non-covalent encapsulation. These nanocarriers formed nanoparticles of different sizes and maintained stability at a neutral pH level. Non-covalent drug carriers showed a faster release pattern, while covalent carriers provided a sustained release, particularly at acidic pH levels [29]. Cellular absorption occurred to a notable extent in monolayer and three-dimensional spheroid cultures of pancreatic cancer cells. PG-co-PCL-based carriers demonstrated significant penetration within 3D spheroids, with non-covalent GEM carriers exhibiting enhanced ability to reach deeply located tumor cells. The cytotoxic effects of GEM-loaded nanocarriers were significantly greater against pancreatic cancer cells than those of free GEM. PG-co-PCL nanocarriers provide a promising drug delivery approach for pancreatic cancer, as their pH-responsive nature allows controlled drug release within the acidic tumor microenvironment [29]. Kutzler and Weiner improve the immunogenicity of DNA vaccines using dendritic cells (DCs) as key antigen-presenting cells. The study aims to enhance the recruitment, expansion, and activation of DCs *in vivo* through co-administration of plasmids encoding macrophage inflammatory protein-1α (MIP-1α) and fms-like tyrosine kinase 3 ligand. This strategy aims to enhance cellular immune responses, optimize antigen presentation, and improve the overall efficacy of DNA vaccines for potential human immunotherapy [30]. DNA vaccination has shown promise in mice, but its effectiveness is limited in humans and nonhuman primates. The mouse model was used to assess the efficacy of simultaneously administering DNA vaccines containing plasmids encoding MIP-1α and Flt3L. The combination strategy results in a more robust antigen-specific immune response. Future research should focus on optimizing adjuvant combinations and validating the approach in nonhuman primates [30].

DC vaccines in cancer immunotherapy, specifically for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), assessed the potential of DC vaccines in cancer immunotherapy, particularly for AML and MDS. The study explores various DC sources, including monocyte-derived DCs and leukemia-derived DCs, which have been used in treatments for AML and MDS. Researchers are investigating the use of DC vaccines in combination with chemotherapy, immune checkpoint inhibitors, and monoclonal antibodies to potentially enhance treatment outcomes. Results from AML clinical trials show that patients vaccinated with DCs exhibit long-lasting, leukemia-targeting immune responses, including a rise in cytotoxic T lymphocytes and increased interferon-gamma secretion. However, challenges such as limited clinical efficacy, cancer cells' ability to evade the immune system, and the need for enhanced vaccine formulations are still needed. Despite these challenges, DC vaccines have emerged as a promising approach in cancer immunotherapy, particularly for AML and MDS. Further clinical trials are needed to optimize vaccine formulations and improve patient selection for treatment [31].

Bolu *et al.* explored the development and application of dendron-polymer conjugates as nanosized drug delivery systems, focusing on self-assembling micellar nanostructures. Dendrimers have a unique branched structure, allowing high drug encapsulation efficiency and biocompatibility. Stable nanosized micelles, ranging from 10 to 200 nanometers, are formed by dendron-polymer conjugates, protecting pharmaceuticals from enzymatic breakdown. Surface modifications such as PEGylation increase solubility and decrease immunogenicity. Drug release can be triggered by external stimuli, with systems for delivering drugs improved with acid-sensitive, enzyme-responsive, and light-activated components. In acidic environments, drug release from pH-sensitive micelles is significantly increased. Dendritic carriers with functionalized properties can enhance targeted accumulation of micelles at tumor sites, such as those with folic acid targeting. Different dendritic architectures display differing efficiencies in drug encapsulation, circulation, and delivery. Dendron-polymer conjugates enhance drug solubility, stability, and controlled release, making them promising carriers for nanomedicine applications. Microcellar nanostructures with stimuli-responsive properties improve targeted drug delivery and reduce off-target toxicity. Future studies should focus on scaling up synthesis, optimizing *in vivo* performance, and clinical translation [32].

Rajput *et al.* investigated the use of dendron-polymer conjugates as self-assembled nanosized drug delivery vehicles, aiming to improve drug solubility, stability, and targeted delivery while reducing toxicity. The InAc-NPs, a nanoparticle-based delivery system for vaccines, target DCs for stimulating cellular immunity. These nanoparticles, about 190 nm in diameter, activate TLR4 on multiple immune cells, secreting various cytokines and promoting DC maturation. In mice, the InAc-NPs produced strong serum antibody titers against the encapsulated antigen (ovalbumin) and generated higher antibody titers even at lower doses. *In vivo* imaging showed that the InAc-NPs provided complete protection in 100% of vaccinated mice from metastasis of intravenously injected melanoma cells to the lungs. The multifunctional InAc-based nanovaccine delivery system has potential

applications in cancer immunotherapy and delivering vaccines against various infectious diseases. Dendron-polymer conjugates offer advantages in drug solubility, stability, and controlled release, making them promising drug delivery platforms. Future challenges include large-scale synthesis, optimizing *in vivo* performance, and clinical translation [33]. Nanotechnology has significantly impacted biology and medicine, leading to the development of supramolecular systems, structures, complexes, and composites. Dendrimers, a type of nanotech polymer, are a notable example of this advancement. Over 100 types of dendrimers have been synthesized, with the most common families being PAMAM, PPI, phosphorus dendrimers, carbosilanedendrimers, and poly(lysine) and poly(L-ornithine) dendrimers. PAMAM dendrimers are based on the ethylenediamine core, while PPI dendrimers are based on a butylenediamine core and PPI monomers. Phosphorus dendrimers contain phosphorus atoms in the core and branches, while carbosilane dendrimers have ammonium or amino groups on the periphery. Dendrimers can improve drug bioavailability by increasing solubility in water and changing surface charge, reducing toxicity. They are beneficial for biomedical applications, including gene therapy applications. However, challenges such as cytotoxicity, biodistribution, and clinical translation remain. Future research should focus on optimizing dendrimer-based therapies and addressing their limitations for broader medical applications [34].

Dendrimers, a class of polymers with a central core, are emerging as a promising solution for ion separation and environmental remediation. These monomers have a complex and highly branched framework with numerous functional terminal groups, resulting in high reactivity and adaptability for a wide range of uses. Their distinctive "dendritic effects" include high solubility, multi-valency, encapsulation capabilities, and size-controlled reactivity. The generation number of a dendrimer influences its properties, with dendrimers of higher generations exhibiting denser and more compact structures, which affect adsorption efficiency. Dendrimers have demonstrated robust affinity for heavy metals, such as Cu^{2+}, Pb^{2+}, Zn^{2+}, and Ni^{2+}.

The metal-binding process is influenced by pH levels, dendrimer generation, and the types of functional groups present. Modified dendrimers increase their ability to bind metal ions and enhance selectivity. Dendrimers supported by a solid base offer an economical and reusable method for metal ion removal. Dendrimers have been investigated for the removal of organic pollutants, such as polycyclic aromatic hydrocarbons and dyes. Their amphiphilic properties enable them to effectively encapsulate both hydrophilic and hydrophobic pollutants. Developments in functionalized dendrimers have been made to enhance adsorption efficiency and selectivity. Overall, dendrimers present a promising and versatile solution to address environmental issues [35].

Gillies and Fréchet explored the potential of dendrimers and dendritic polymers in drug delivery, particularly in cancer treatment. Dendrimers, such as PAMAM, polylysine, and polyaryl ether dendrimers, have been developed to enhance drug solubility, biodistribution, and targeted delivery. They have shown promise for safe drug delivery applications, such as polyester-based and carbohydrate-functionalized versions. Anticancer drug delivery is being investigated using dendrimers in covalent conjugation and noncovalent encapsulation. Covalent conjugation provides a more reliable drug delivery method, while dendrimers functionalized with folate show promise for tumor-specific targeting. Boron neutron capture therapy uses boronated dendrimers to deliver boron-10 to tumors, but their therapeutic efficacy has been limited due to liver accumulation. Tumor targeting has been enhanced by modifications such as polyethylene oxide shielding and folate conjugation, but further work is needed. In photodynamic therapy, dendrimers have been investigated as carriers for photosensitizers. Studies show that dendrimers enhance photosensitizer solubility and targeted distribution, and recent methods such as two-photon excitation dendrimers, offer improved treatment outcomes and deeper tissue penetration. Despite their significant potential in drug delivery, challenges remain in optimizing biodistribution, drug release mechanisms, and large-scale synthesis. Further research is needed to enhance their clinical applicability, especially in long-circulating drug carriers [36].

Romero *et al.* examined the effectiveness of dendritic glycerol-cholesterol amphiphiles as drug delivery systems by comparing monomeric and polymeric structures. The primary goal is to evaluate their biocompatibility, aggregation behavior in aqueous solutions, and potential for solubilizing hydrophobic drugs. The polymeric system consists of non-ionic polymeric amphiphiles synthesized via sequential RAFT polymerization of polyglycerol first-generation dendron methacrylate and cholesterol methacrylate, while the monomeric system is a polyglycerol second-generation dendron end-capped to a cholesterol unit. Both amphiphiles form spherical micellar aggregations in aqueous solution, with differences in size and morphology for hydrophobic molecules. The polymeric system showed a lower critical micelle concentration (CMC) of 0.2 μg/mL compared to the monomeric system (17 μg/mL). Cytotoxicity assays showed that the polymeric system had significantly higher cell viability than the monomeric amphiphiles. The polymeric micelles were used as drug delivery systems by encapsulating hydrophobic small molecule DOX, achieving a loading capacity of 4%. The findings highlight the advantages of polymeric amphiphiles over monomeric counterparts in drug delivery applications, offering better biocompatibility, lower CMC, and effective drug encapsulation. Using cholesterol as a building block in polymer synthesis appears to be a promising strategy for developing efficient and safe drug carriers (Figs. 1-3) [38].

Aida *et al.* explored the synthesis, functionalization, and self-assembly of supramolecular dendritic polymers (SDPs), a type of non-covalently bound, highly branching macromolecule with a three-dimensional global architecture [39]. SDPs are attractive for smart materials and drug delivery systems due to their dynamic and reversible properties, distinct topological structure, and outstanding physical/chemical characteristics. They can dynamically switch structure, morphology, and function in response to external stimuli, making them a versatile platform for designing and producing smart supramolecular polymeric materials and functional supramolecular devices. SDPs are classified into six major types based on their topological features: supramolecular dendrimers, dendronized polymers, hyperbranched polymers, linear-dendritic block copolymers, and supramolecular dendritic multiarm copolymers.

Non-covalent interactions, such as hydrogen bonding, π-π stacking, and host-guest interactions, enable SDPs to self-assemble into various hierarchical structures, such as micelles, vesicles, fibers, and other hierarchical structures. These properties enable SDPs to function as drug and gene delivery vehicles, bioimaging agents, and nanoreactors. The study also examines current advances in SDP functionalization, including terminal, focal-point, and backbone alterations, which improve their flexibility in biological and industrial applications. However, challenges such as reliability, scalability, and practical application integration remain a critical topic [40].

The discovery of these materials dates back to the late 1970s when Donald Tomalia, et.al., and their team at Dow Chemical created the first PAMAM dendrimers. Researchers such as Buhleier and Newkome made significant contributions to the field, enhancing the synthesis of dendritic polymers. Over the years, two primary synthetic methodologies have been developed to produce monodispersed and well-defined dendritic architectures. Dendrimers' distinctive characteristics, such as highly functionalized surfaces, internal cavities, and customizable structures, make them excellent candidates for various applications in nanotechnology, biomedicine, and materials science. Their potential in drug delivery, dental biomaterials, and supramolecular chemistry has been thoroughly investigated, highlighting their capabilities in targeted therapies, biomimetic remineralization, and controlled drug

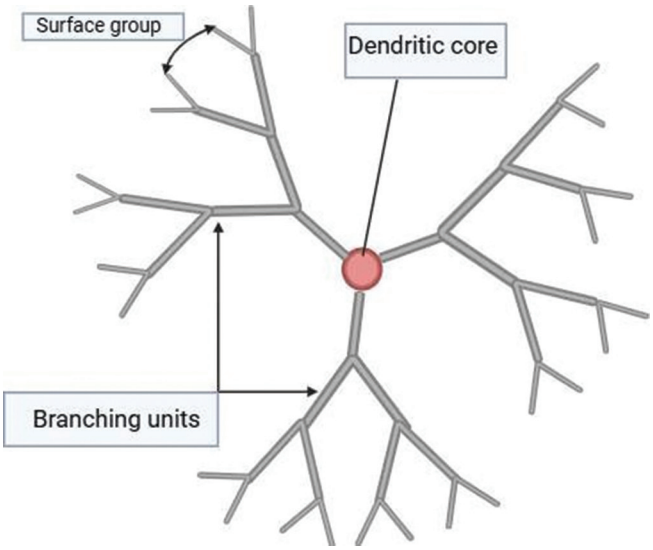


Fig. 1: Dendrimer structure

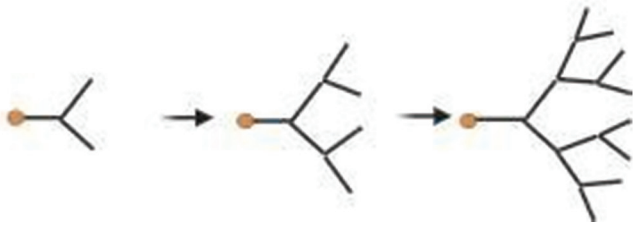


Fig. 2: Convergent method

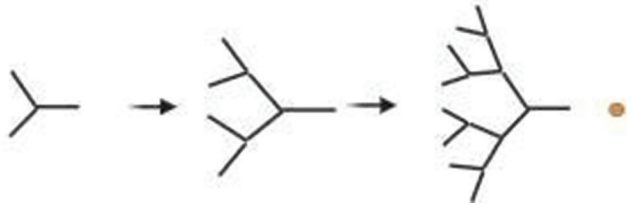


Fig. 3: Divergent method

release. Mass spectrometric (MS) methods for protein characterization have enhanced the recognition of dendrimers as distinct entities with exceptional structural accuracy [41,42]. PAMAM dendrimers play a significant role in biological structures that are conserved and vital in the life sciences. The advent of conventional synthetic polymer architectures, such as linear and crosslinked forms, laid the groundwork for substituting natural polymers, including silk, rubber, and cotton, while also presenting various enhancements and benefits [43-45].

Newkome *et al.* explored the potential of dendrimers, synthetic, highly branched, monodisperse macromolecules at the nanometer scale, for drug delivery. The study focuses on their structural characteristics, synthesis methods, functionalization techniques, and effectiveness in enhancing drug solubility, targeting precision, and controlled release mechanisms. It also evaluates biocompatibility, biodistribution, and safety issues related to dendrimers to determine their clinical viability. Dendrimers have gained attention since the mid-1980s due to their consistent size, water solubility, customizable surface properties, and internal cavities. The research provides an in-depth examination of dendrimers, with a particular focus on PAMAM dendrimers. It also discusses potential challenges, such as toxicity and biodistribution issues [46].

A macromolecular drug-delivery system is a complex material where a drug is linked to a carrier molecule, such as a synthetic polymer, antibody, hormone, or liposome. The carrier's properties influence the absorption and distribution of the drug, allowing for optimization of site specificity, protection against degradation, and side effects. An ideal carrier should be biochemically inert and non-toxic, ensuring the drug is protected until it reaches its target site [47]. Polymeric drug-delivery systems have been developed over time, with polymeric micelles serving as a conceptual framework for drug delivery. Dendrimers, highly branched, monodisperse macromolecules with tunable surface functionality and internal cavities, are ideal candidates for drug delivery. PAMAM dendrimers have been extensively studied due to their biocompatibility, water solubility, and ability to encapsulate or conjugate drugs. They offer improved drug solubility, targeted delivery, and controlled drug release through pH-sensitive or enzymatic mechanisms. However, challenges such as cytotoxicity, hemolysis, and biodistribution remain, particularly for cationic dendrimers. Structural modifications, such as PEGylation or surface neutralization, have been investigated to enhance biocompatibility and reduce side effects [48].

Polymeric prodrugs can be used to bypass the multidrug resistance phenomenon in cancer cells by utilizing the endocytotic mechanism of cell uptake [49,50]. The higher molecular weight of the conjugate affects the drug's pharmacokinetics, making it more accessible for accumulation in target tissue, increasing the potential for improved delivery and effectiveness [51,52]. High molecular weight systems offer advantages over low molecular weight molecules, resulting in enhanced targeting of tumor tissue and treatment efficiency. This is due to the enhanced permeability and retention (EPR) phenomenon observed in tumor tissue, which allows for selective targeting and limited access to lymphatic capillaries via the tumor, limiting macromolecule accumulation. The coupling of an active drug to the appropriate polymeric backbone may overcome water solubility problems and lower the toxicity of the drug until it is delivered to the target tissue. The higher molecular weight of the conjugate also affects the pharmacokinetics of the drug, making the polymeric prodrug more accessible for accumulation in the target tissue, increasing the possibilities of improved delivery and efficacy.

RESULTS

Dendritic structures, including PAMAM and peptide dendrimers, have over 100 different structures with various sizes and molecular weights, demonstrating their versatility and potential applications. Lower-generation dendrimers penetrate the skin more efficiently than higher generations, making them useful for transdermal drug delivery. Dendritic micelles can encapsulate DOX at loading capacities up to 95%, enhancing drug delivery potential. In mouse studies, drug-loaded dendritic micelles were 1.5 times more effective in suppressing tumor growth than free DOX, indicating enhanced cancer therapy efficacy. Dendron-polymer conjugates form stable micelles sized between 10 and 200 nm, essential for drug protection and controlled release. Nanoparticles showed minimal toxicity and were cleared from the injection site within 30 h, assessing biocompatibility. Inulin acetate nanoparticles (InAc-NPs) have a diameter of approximately 190 nm, aiding in targeting DCs for immune response stimulation. High molecular weight polymeric systems enhance drug delivery through the enhanced permeability and retention effect in tumors.

CONCLUSION

Dendrimers represent a highly versatile class of nanostructured carriers with over 100 documented structures, showcasing their adaptability for various biomedical applications, particularly in drug delivery and nanomedicine. The unique properties of dendrimers, such as their nanoscale size, high drug encapsulation capacity, and ability to penetrate biological barriers, significantly enhance the solubility, stability, and efficacy of therapeutic agents. For instance,

Number	Dosage form	Use in a novel drug delivery system	References
1	Transdermal delivery	Offers painless drug administration due to skin's large surface area and systemic access through circulatory and lymphatic networks	[61]
2	Nanocarriers for drug delivery	Dendrimers function as carriers for drugs, improving solubility, stability, and bioavailability.	[62]
3	Polymeric nanoparticles	Polymeric nanoparticles improve drug bioavailability and specific delivery. Versatility of polymers makes them ideal for specific drug-delivery systems.	[62]
4	Dendritic polymer-based nanoparticles	Facilitate deep tumor penetration, enhance the therapeutic effect, and improve drug diffusion within the dense extracellular matrix of solid tumors	[63]
5	Micelles	Provide controlled and stimulus-responsive drug release, particularly in response to pH changes.	[64]
6	Nanoscale	Nanomedicines provide potential drug delivery to human organs previously beyond microscale drugs' reach. Nanoscale systems function as nanocarriers for drug delivery, made of biocompatible and biodegradable materials	[65]
7	DNA vaccines	Utilizing various physical and chemical methods to enhance DNA uptake in cells improving treatment precision.	[66]
8	Injectable solutions	Facilitate the controlled release of a drug over an extended period, enhancing therapeutic efficacy, safety, and administration convenience.	[67]
9	Transdermal patches	To optimize drug flux through the skin into systemic circulation while minimizing its retention and metabolism within the skin	[68]
10	Biosensor	monitoring environmental pollution, detecting toxic elements, identifying biohazardous viruses or bacteria in organic matter, and analyzing biomolecules in clinical diagnostics.	[69]
11	Liposomes	Enhance drug solubility and controlled distribution, along with their potential for surface modifications to achieve targeted, prolonged, and sustained release.	[70]
12	Nanotubes	Potential for functionalization to achieve site-specific drug release.	[71]
13	Micelles	Enables selective delivery to specific tissues, reducing systemic side effects.	[72]

Brand Name	Manufacturer	Inventor	Uses
VivaGel®BV	StarPharma	Dr. Jackie Fairley, Dr. David McGinness	Treat and prevent bacterial vaginosis, i.e., vaginal odor and discharge [73].
Stratus CS Acute Care™	Siemens Healthcare Diagnostics	James P. Henderson, Thomas E. Eisinger, Klaus G. Hochberg, Wolfgang H. Hauck, Michael J. Shanahan	accurate evaluation of patients presenting with suspected myocardial ischemia [74].
VivaGel®	StarPharma	Dr. Jackie Fairley, Dr. David McGinness	Act as an Antiviral agent [75].
SuperFect™	Qiagen	Dr. Hans-Helmut Gerdes	Delivers DNA vaccines in cells [76]
Priostar™	Starpharma	Dr. John R. Whitehead, Dr. Ian R. Whittaker, Dr. Terry P. McCarthy	Improve solubility and bioavailability of anticancer drugs as well as antibiotic and anti-inflammatory drugs [77]

Drug Name	Inventor	FDA approval date	Patent number	References
Transdermal delivery	Nathan Fitzsimmons Ryan Beal Audrene McMahon Brandon Sand Kilmar Martinez	Nov 24, 2020	US10842758B1	[78]
Nanocarrier for drug delivery	Matthias Stephan.Howell F. Moffett	Aug 29, 2024	US20240285797A1	[79]
Polymeric nanoparticles	Harpal Singh	Jun 9, 2022	US20220175874A1	[80]
Dendritic polymer base nanoparticles	Mamadou S. Diallo. Madhusudhana Rao KOTTE. Alex KUVAREGA	Jun 25, 2024	US12017188B2	[81]
Micelles	Janni Mirosevich, Gregoire Cardoen, Kevin N. Sill, Habib Skaff	Jun 10, 2024	US8747904B2	[82]
Nanoscale	Asmamaw Wassie, Fei Chen, Edward Stuart Boyden, Shahar Alon, George Church, Evan Daugharthy.	Feb 13, 2024	CA2994958C	[83]
DNA vaccine	Hso-Chi Chaung, Li- Hsiang Hung, Yi-Yang Lien.	July 6, 2010	US7749979B2	[84]
Injectable solution	David Duracher, Gregory Meiffren, Remi Soula	July 25,2023	US11707507B2	[85]

PAMAM dendrimers and dendritic micelles have demonstrated remarkable capabilities in encapsulating drugs like DOX, leading to improved therapeutic outcomes in cancer treatment. The development of dendron-polymer conjugates and other dendritic systems with controlled molecular architectures and low polydispersity indices ensures consistent and reproducible drug delivery behaviors. This is crucial for clinical applications where uniformity in drug delivery is essential. The favorable biocompatibility and rapid clearance of dendrimer-based nanoparticles from the body highlight their potential for safe and effective therapeutic use. Their ability to minimize toxicity while maximizing drug delivery efficiency is a significant advantage in developing new treatment modalities.

FUTURE DIRECTIONS

Continued research and development are necessary to optimize dendrimer formulations, enhance their targeting capabilities, and address challenges related to toxicity and biodistribution. The

integration of dendrimers in combination therapies and their application in emerging fields such as gene therapy and vaccine delivery further underscores their transformative potential in modern medicine.

AUTHOR CONTRIBUTION STATEMENT

"The first draft of the manuscript was written by Sayali Vilas Khaladkar and Rutuja Anna Rahatal. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

DECLARATION OF INTEREST STATEMENT

All the authors declare that they have no established conflicting financial interests or personal relationships that may have influenced the research presented in this paper.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this review article.

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