WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 14, 138-155. Review Article ISSN 2277–7105

A REVIEW ON DENDRIMERS: SYNTHESIS, CHARACTERIZATION, PROPERTIES, TYPES, AND BIOMEDICAL APPLICATIONS

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Article Received on
23 May 2024,

Revised on 13 June 2024,
Accepted on 03 July 2024

DOI: 10.20959/wjpr202414-32761

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ABSTRACT

This study offers a concise overview of dendrimers, including their production, characterization, and use in drug administration. Dendrimers have distinct molecular weights, sizes, shapes, and monodispersities. Due of these characteristics, dendrimers are a good carrier for applications involving drug delivery. The solubility of medications that are weakly soluble is increased by dendrimers, which are composed of several molecular entities of colloidal particles that exist in equilibrium with the molecules or ions in nature. Their unique structural design has given these better chemical and physical qualities. They are more adaptable since DNA, heparin, and polyanions are compatible. Molecules can self-assemble to create nanoscopic functional and structural systems more quickly. However, assessing their true efficacy in drug delivery requires acknowledging their in vivo behavior. Research has looked into the biological potential of dendrimers, including gene transfer, vaccine development, and the creation of antiviral, antibacterial, and anticancer treatments. Additionally, this article explains how the dendrimers have interactions with many medications, as well as the potential for these macromolecules to work with drug nanocarriers in the transdermal, ocular, respiratory, oral, and intravenous routes of delivery. For biomedicine, dendrimers guarantee improved potential protrusion. The physico-chemical characteristics of dendrimers and their possible applications in several fields of study, technology, and medicine are briefly covered in this overview.

KEYWORDS: Dendrimer, Synthesis, Characterization, Properties, Application.

INTRODUCTION

The Greek terms δένδρον, or dendros, meaning "part of" for their chemical memory and meros, meaning "tree-like," are the source of the name "dendrimer" structure created by using more monomers.[1] The polypropylene-imine (PPI) polymer was first described in a paper by Fritz Vögtle, Fried Wehner, and Egon Buhleier in 1978. PPI was described as "capable of binding ionic guests or molecules in a Host-Guest interaction, and obtained through a synthetic pathway allowing a frequent repetition of similar steps."

The synthesis of "starburst dendritic macromolecules" and "nanocascade spheres" was described in 1985, revealing a new class of macromolecules that are now known as dendrimers[2] which were created by repeatedly adding monomers and activating the resulting branching molecules.[3]

Dendrimers, also known as dendritic polymers, are nanoparticles with a diameter ranging from 1 nm to 100 nm that are occasionally employed as drug delivery vehicles.[4,5] By making drugs more soluble, these nanodelivery systems can raise their bioavailability. Furthermore, by extending the duration of medication exposure, they can minimize the negative effects of the medicine and lower the therapeutic dosage.[6]

Dendrimers are hyperbranched, monodisperse, three-dimensional structures with a center encircled by peripheral groups. Their physicochemical and biological characteristics are essentially derived from these features. Typically, dendrimers have three unique architectural elements, as seen in **Figure 1**: core, branches (an inner layer made up of repeated units tied to the core), and terminal groups connected to the branches are the three main components.[2] The medication's solubility and stability are increased by the dendritic polymer structure, which forms interior cavities in which the drug can be deposited. These macromolecules are attractive candidates for use as pharmacological excipients due to the previously mentioned qualities.[7,8]

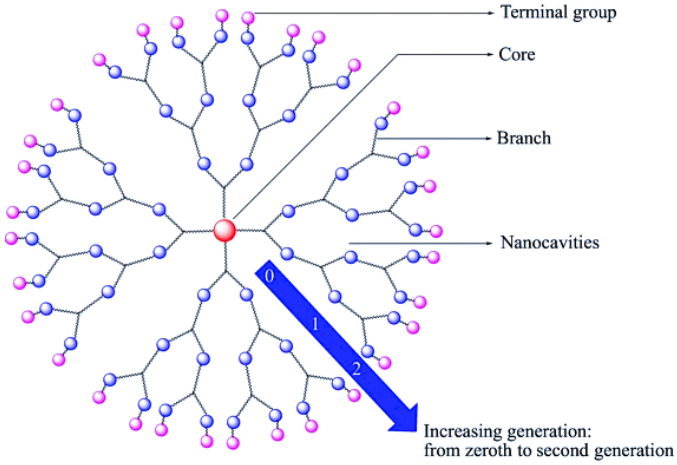

Figure 1: Basic structure of a dendrimer.

Dendrimers have many uses that stem from the inherent properties of polymers as well as, and particularly, from their attributes: porosity, accessibility to the core, presence of functionalized cavities, accessibility to the surface, on-surface easily accessible functions, and of course multivalency and cooperativity.[9]

Dendrimers are incredibly versatile materials that may be modified in terms of their morphology, porosity, structure, and flexibility. Chemical synthesis, analysis, catalysis, materials science (Films, layers, and hybrids), pharmacy (Drugs, medicine), nanosciences (Nanoparticles), biology, and medicine (Immunology) are all relevant to their applications.[10]

Because they have several surface functional groups that can be used to target or label the dendrimer for imaging and drug delivery applications, dendrimers are extensively studied and employed in biomedical applications.[11]

Synthesis

Dendrimers are composed of three main components: an outer shell, an inner shell, and a core. By changing the functionality in each of these sections, a dendrimer can be created to classify attributes like solubility, thermal stability, and the addition of substances for careful application.[12]

The first synthesized dendrimers were PAMAMs, introduced in 1980. Later on, however, a number of other dendrimers were created, such as glycodendrimers, polyester dendrimers, amphiphilic dendrimers, poly(propyleneimine) (PPI) and poly-L-lysine (PLL).[13]

Classical synthesis pathways

Dendrimers are often produced using techniques that enable structural control during the whole building process. The dendritic structures are mostly synthesized by two main different methods: divergent and convergent.[11]

Divergent growth method

According to the divergent approach, the dendrimer is created from the core, which serves as the beginning point, and is constructed outward from generation to generation (Fig. 1.3). In order to create the first generation G1, an AB2 unit is coupled to the central core. The next step involves a series of "activation-coupling" reactions to produce the second generation G2. Higher generations, or "Gn," can be synthesized through the recurrence of such a pattern.[11]
To prevent inadequately produced branches in the divergent method, it is crucial that all reaction steps be finished before adding a new generation.[14]

The divergent technique typically results in the synthesis of molecules of dendrimers with high degrees of symmetry. But lately, scientists have focused on the potential of using the divergent growth approach to produce heterogeneously functionalized dendrimers, which results in dendrimers with a variety of functional groups attached to the surface.[15]

Convergent growth method

Hawker and Fréchet were the first to establish such a technique in1989 -1990.[16,17] Through a "coupling and activation" sequence, the branches of different generations are synthesized and subsequently linked to the functional core (Fig.2). Few secondary reactions and relatively defect-free structures result from the convergent growth, which involves a limited number of reactive sites in each reaction step. Even if purification gets more difficult with each successive generation, it is still possible to cleanse any so-obtained generation with ease. However, one problem is related to the reactive groups' core position: for higher generations, the focal point becomes increasingly buried by branches and isolated, which reduces reactivity.

Although there are comparatively fewer coupling reactions at each growth stage in convergent synthesis compared to the divergent method, more structural control may be accomplished, enabling the synthesis of dendritic products with unparalleled purity. Furthermore, this method makes it possible to synthesize asymmetric dendrimers, or JDs (“Janus” dendrimers) by coupling various segments to produce dendrimers with diverse

morphologies. Owing to the previously mentioned benefits, this synthesis method offers up interesting possibilities for combining multiple active sites into a single dendrimer to produce multifunctional excipients.[15]

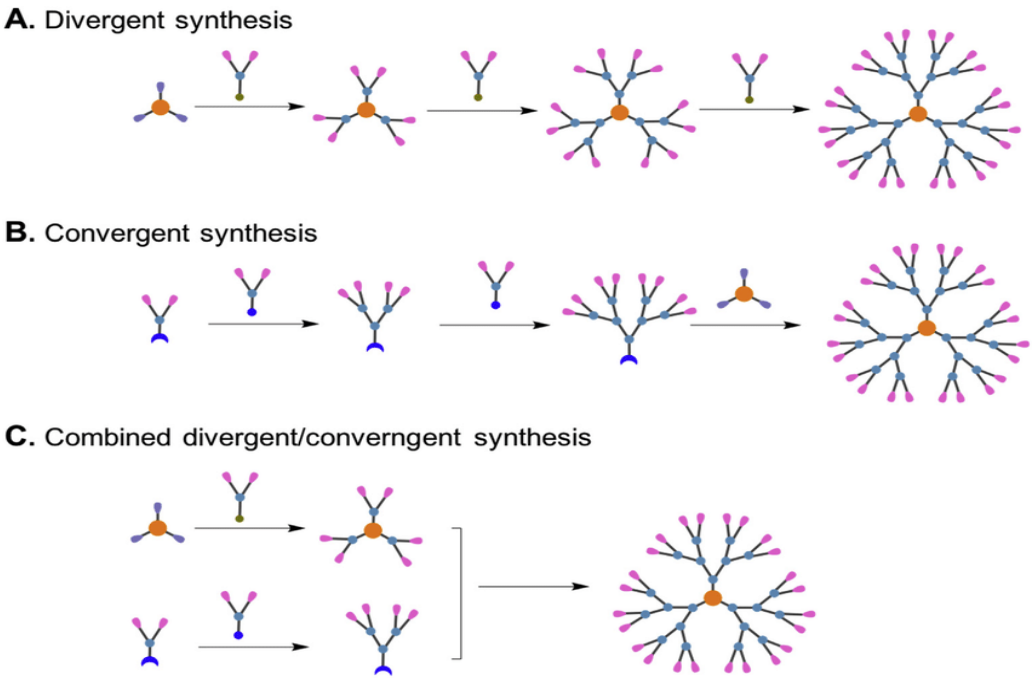

Figure 2: Divergent method and convergent method of dendrimer synthesis.

Factors affecting dendrimers synthesis

There are different factors which can affect dendrimer synthesis. The non-ideal dendrimer expansion may be manifested through a variety of ways which include:

1. Incomplete addition reaction.
2. Intermolecular cyclization.
3. Fragmentation.
4. Solvolysis of terminal functionalities.

Characterization of dendrimer

The well-defined nanometric architecture of dendrimers results from the controlled synthesis of these moieties at each step through chemical reactions. Characterization of dendrimers is thus a crucial step in the design and engineering of these versatile nanoscopic carriers.[46,47]

Dendrimer characterizations using a variety of techniques are shown in **table 1** below.

Table 1: Characterization of dendrimers.[48]

Analytical methods	Characterization parameter
Nuclear magnetic resonance (NMR)	It aids in identifying the chemical changes that end groups experience, making it useful for structural investigation of dendrimers and meticulous characterization of synthesis.
Infrared spectroscopy and Raman spectroscopy	It ascertains the chemical transformation taking place during the synthesis or surface engineering of dendrimers
X-ray diffraction	Chemical composition, size and shape
UV–visible spectroscopy	It helps in determining the change in chemical structure and synthesis method by detecting chromophores and auxochromes. Also used to test the purity of dendrimers
Fluorescence	It is used to characterize the structure and synthesis of dendrimers having photochemical groups and to quantify defects occurred during the synthesis
Circular dichroism	Characterization of structure of dendrimers having optical activity
Atomic force microscopy	Size, shape and structure
Transmission electron microscopy	Size, shape and structure
Electron paramagnetic resonance	Surface structure
Small-angle X-ray scattering (SAXS)	It gives average radius of gyration (Rg) in solution hence used for determination of average particle size, shape, distribution, and surface-to-volume ratio
Small-angle neutron scattering (SANS)	It yields an average radius of gyration (Rg) in the solution and detailed insights into the internal structure of the entire dendrimer.
X-ray photoelectron spectroscopy	Chemical composition and size
Electrochemistry	It gives information about the structure of dendrimers
Electrophoresis	Purity and homogeneity of water-soluble dendrimers
Laser light scattering (LLS)	Hydrodynamic radius of dendrimers
Mass spectrometry (FAB-MS, ESI-MS, FT-ICR MS, MALDI-TOF MS)	Determination of molecular mass and some structure information
Size exclusion (or Gel permeation) chromatography (SEC) (GPC)	Molecular weight and size
Intrinsic viscosity	Physical characterization and morphological structure
Differential scanning calorimetry (DSC)	Glass transition temperature (Tg), which is affected by the molecular weight, entanglement and chain-end composition of polymers
Dielectric spectroscopy	Study of molecular dynamics

Physicochemical properties

Dendrimers are a relatively new family of molecules distinguished by their distinct dimensions and molecular architecture. Dendrimers have several advantages over other delivery systems, such as: (i) their three-dimensional and globular architecture; (ii) their controllable structure and size; (iii) their lower molecular volume when compared to linear polymers of similar molecular weight; and (iv) their ideal suitability for a wide range of applications, including drug encapsulation.[18,19] These nanosystems also possess significant physicochemical characteristics that make them attractive options for excipients in medicinal products. An examination of the physicochemical characteristics of dendrimers is required in order to fully comprehend their potential as pharmacological excipients. Several properties of dendrimer are listed below in the given **Table 2.**

Table 2: Properties of dendrimer.[49]

S. No.	Properties	Dendrimer
1	Structure	Compact and Globular
2	Shape	Spherical
3	Architecture	Regular
4	Structural control	Very high
5	Synthesis	Stepwise growth
6	Crystallinity	Non-crystalline and amorphous materials Lower glass temperatures
7	Reactivity	High
8	Aqueous solubility	High
9	Nonpolar solubility	High
10	Viscosity	Low
11	Ionic conductivity	High
12	Compressibility	Low
13	Polydispersity	Monodisperse

Types of dendrimers

pamam (Poly amido amine) Dendrimers

PAMAM dendrimers are the first dendrimers that have been extensively investigated for their potential biomedical applications.[20] These have an elliptical or spheroidal form.[21] Because of the prevalence of several functional end groups and unfilled interior cavities, it possesses high solubility and reactivity.[22,23] The Tomalia group initially created PAMAM dendrimers by growing amidoamine units from an amine-functional core using a divergent technique.[24] The surface's abundance of primary amine groups facilitates complexation with negatively charged nucleic acids for gene transport in addition to allowing for the conjugation of several

bioactive compounds.[25] PAMAM dendrimers are the topic of lengthy assessments that may be obtained elsewhere due to their lengthy development history.[26–29]

PPI (Poly propylene imine) Dendrimer

PPI dendrimers are made from a 1,4-diaminobutane (DAB) core. They are also referred to as DAB dendrimers.[15] Primary amines serve as terminal groups and tertiary propylene amines serve as the center of its Di amino butane-based core structure. These are widely utilized in biology and material science, and they are commercially accessible up to G-5.[30] The divergent growth method stands as a fundamental approach in the synthesis of dendrimers such as PPI, providing a key strategy for their creation. A series of repeated double Michael additions of acrylonitrile to primary amines, followed by a reduction of the nitriles to produce surface primary amines, regulate their outward development.[15] The divergent growth method stands as a fundamental approach in the synthesis of dendrimers such as PPI, providing a key strategy for their creation.

Glycodendrimers

Glycodendrimers are a relatively recent class of synthetic biomacromolecules, having made their debut in 1993.[31] Glycodendrimers are primarily characterized as dendritic molecular structures that have surface modifications to create saccharide termini or saccharide blocks.[32]

Glycodendrimers are dendrimers where the branches are composed of glycan molecules or derivatives thereof. These dendrimers are often synthesized by attaching carbohydrate units to a core molecule and then sequentially adding more branches. Glycodendrimers have garnered interest due to their potential applications in areas such as drug delivery, molecular recognition, and vaccine development. Their carbohydrate moieties can interact with various biological receptors, making them valuable tools for studying carbohydrate-protein interactions and for designing targeted therapeutics.

Phosphorous dendrimers

The chemistry of phosphorus is crucial for mediating the various biological processes that occur within the body. Numerous signaling pathways depend on phosphorylation, and phosphorous element is found in cell membranes, bones, and the genetic code. As a result, dendrimers with phosphorous component have generated a lot of interest. The best studied of

these are poly(phosphorhydrazone) (PPH) dendrimers, which were initially created by Majoral and colleagues and include a cyclotriphosphazene core.[33]

Aza-bisphosphonate (ABP)-capped phosphorous dendrimers have drawn attention among the many modified phosphorous dendrimers that have been reported because of their intriguing self-owned bioactivities involving the immune cells. In order to create various types of nanoplatforms for improved drug or gene delivery toward cancer management, it has been demonstrated in recent years that it is possible to modify various cyclic amines, such as pyrrolidine, morpholine, methyl piperazine, and phenyl piperazine, onto the phosphorous dendrimer surface and incorporate different metal elements. Majoral, Mignani, Caminade et al. have provided excellent reviews that outline the production method and biological uses of phosphorous dendrimers.[34-38]

Tecto dendrimers

These were composed of core dendrimers that can be encircled by additional dendrimers that carry out a particular task, resulting in an intelligent therapeutic system that is utilized to identify the unhealthy condition and supply API to the acknowledged diseased cell.[39]

Peptide dendrimers

Amino acids are held in peptide dendrimers as internal or branching units. These are utilized in the delivery of vaccines and for diagnostic purposes.[40]

Peptide dendrimers are made of short chains of amino acids, which are commonly used as peptide building blocks in dendrimer construction. Peptide branches extending outward from a central core molecule characterize the structure of peptide dendrimers. These branches can be carefully and methodically extended to produce dendrimers with distinct structures.

PLL Dendrimers

PLL dendrimers have positively charged primary amine terminal groups and a somewhat neutral inner structure, similar to PAMAM and PPI dendrimers. Interestingly, because the two main amine groups of L-lysine are situated on the two termini of an asymmetrical branched alkyl chain, PLL dendrimers are not totally symmetrical. It appears that their structural qualities are unaffected by their unique topology, nevertheless. Falkovich et al. have demonstrated that asymmetric PLL dendrimers and dendrimers with symmetric

branching share comparable structural characteristics, such as the radius of gyration and shape anisotropy.[41]

PLL dendrimers are thought to be an exemplar of peptide dendrimers. Usually, they are made by conjugating tert-Butyloxycarbonyl (tBOC)-protected L-lysine to an amine functional core, then de-protecting the BOC to produce new main amine sites for the chain's further outgrowth.[42]

PAMAM-organosilicon (PAMAMOS) dendrimers

Radially layered PAMAMOS dendrimers (PAMAMOS) are inverted unimolecular micelles with hydrophilic, nucleophilic PAMAM inside and hydrophobic organosilicon (OS) exteriors. PAMAMOS dendrimers have special qualities that make them ideal for new applications in chemical catalysis, photonics, electronics, and nano-lithography. These include their ability to form complex structures and to precisely encapsulate different guest species at the nanoscopic topological level.[45]

The development and investigation of various types of dendrimers, such as polyether dendrimers, polyester dendrimers, triazine dendrimers, melamine dendrimers, citric acid dendrimers, etc. using different core and branching units, is prompted by the constant demand for the optimal therapeutic delivery system or the various medications used in the treatment of infectious and non-infectious diseases. The field of dendrimers is constantly growing, and the uses for this adaptable carrier technology in medication delivery are growing every day.

Biomedical applications of dendrimer

Due to its distinct size, dendrimers have drawn interest from researchers for use in biological applications such as gene transfection, controlled distribution of bioactives, and imaging and diagnostic agents. Among the special qualities that make dendrimers the best option for use in the biomedical area are their nanometric size, broad branching, tailor-made surface groups, monodispersity, and exceptional stability. Numerous scientists have examined the various biomedical uses of dendrimers, such as vaccinations, diagnostic agents, gene transfer, etc.[50,51]

Dendrimers in gene delivery

Gene transfer, which includes introducing new genetic material to a host in order to treat disease, is a priceless experimental tool. Therapeutic nucleic acid delivery in vivo has been

documented using a variety of physical techniques and vectors. Typically, two methods: viral and non-viral are employed to enable the effective transfer of genetic material to target cells. Virus carriers can transfect cells quickly, yet there is still cause for concern regarding the immunological and cancerous side effects these vectors may cause. Non-viral gene delivery vectors allow genetic material to be transferred to specified cells by the use of physical forces or natural or manmade chemicals. Non-viral vectors are preferred for gene therapy due to their many benefits, including low immune response, targeting capabilities, ease of manufacture, and potential for repeat delivery. Santos and colleagues conducted a thorough analysis of different physical and chemical techniques for non-viral gene delivery, dendrimer-based vectors, and their uses in tissue engineering and regeneration.[43] PAMAM dendrimers, which are commercially accessible, have garnered significant attention as prospective non-viral gene delivery vehicles owing to their cationic character, which facilitates DNA binding at physiological pH.[44]

Intracellular delivery of bioactives

Their ability to transfer molecules at the intracellular level is one of the most exciting uses of. Scientists have used them to target intracellular levels through the intracellular delivery of medications. Antiviral medication targeting of macrophages has been made possible by dendrimers surface-engineered with mannose to facilitate endocytosis by the mannose receptor.[52]

Enhanced uptake of dendrimers with consequent release of anti-cancer agent into cancer cells has been reported by many scientists.[53,54] In order to achieve intracellular delivery of bioactive substances, it is imperative to reduce extracellular leakages. This can be achieved by preventing dendrimers from interacting non-specifically with systemic circulation and by making sure that the drug-loaded nanometric dendritic system won't be rapidly cleared from the systemic compartment. Human cancer epithelial cell line uptake was enhanced by conjugating PAMAM dendrimers with methylprednisolone. The dendritic complex's activity was shown to be comparable to free drug in this investigation.[55]

It has also been noted that in certain drug dendrimeric complexes, the drug is swiftly absorbed by the target despite the drug being released gradually over an extended period of time. Kolhe et al. found that A549 cells quickly absorbed PAMAM dendrimers that were complexed with ibuprofen. Ibuprofen covalently coupled demonstrated the prolonged release.

It was determined that dendrimers and surface-engineered dendritic nano-architectures might be effectively utilized for targeting therapeutic compounds at the intracellular level.[56]

Dendrimers as nanoscale containers (Nano-scaffolds)

The three parts of dendrimers the core, inner branching, and specially designed surface groups represent the potential carriers of bioactive substances. In particular, pharmaceuticals can be efficiently encapsulated in the internal cavities of dendrimers as guest molecules, with the dendrimers acting as hosts. For targeted distribution, the dendrimer surface groups that are exposed to the outside are essential.[57]

Dendritic boxes are made by surface-modifying poly(propyleneimine) (PPI) dendrimers with amino acids. Dense, hydrogen-bonded surface shells with exceptional trapping capabilities and solid-state features set these boxes apart. The size, shape, and accessibility of the interior cavities of the dendrimers, as well as the form and size of the molecules to be encapsulated within the dendrimers, both affect the encapsulation effectiveness of these molecules. For example, it has been demonstrated that a PPI dendrimer with twelve small and four large cavities may encapsulate eight to ten small bioactive compounds, like p-nitrobenzoic acid, without leaking.

In contrast, these dendrimers can accommodate only four molecules of large bioactives, such as Rose Bengal dye.[58,50]

Microvascular extravasation

Dendrimers have a tendency to extravasate, which is the movement of molecules from the blood circulatory system via the endothelium lining of capillary walls and into the surrounding interstitial tissues. This is because of their nanometric size and reduced molecular weight.[59]

For therapeutic compounds to be delivered to specific targets effectively, extravasation is essential. Kitchens et al. studied the extravasation of different generations of PAMAM dendrimers across the microvascular endothelium and found that the size and molecular weight of the dendrimers, in the following order: 0.0 G < 1.0 G < 2.0 G < 3.0 G < 4.0 G, are exponentially related to the extravasation time. The extravasation time was found to vary between 143.9 and 422.7 seconds.[60] Microvascular extravasation plays a crucial role in the

passive localization of anticancer bioactives and the diagnosis of cancer using MRI contrast agents, among other applications.[61,62]

CONCLUSION

In conclusion, dendrimers represent a promising avenue in the field of drug delivery and biomedical applications. Their unique molecular architecture, characterized by distinct sizes, shapes, and monodispersities, offers numerous advantages for drug encapsulation and delivery. Dendrimers enhance the solubility of poorly soluble medications, thereby increasing their bioavailability and reducing therapeutic dosage requirements. Moreover, their hyperbranched structure provides opportunities for functionalization, allowing for precise control over their physicochemical properties and surface functionalities.

While dendrimers hold immense potential as drug carriers, their true efficacy in drug delivery hinges on their in vivo behavior. Research efforts have explored various biomedical applications of dendrimers, including gene transfer, vaccine development, and the creation of antiviral, antibacterial, and anticancer treatments. Additionally, dendrimers exhibit interactions with a wide range of medications and offer potential in conjunction with drug nanocarriers for diverse routes of administration.

The synthesis of dendrimers has been predominantly achieved through divergent and convergent growth methods, enabling precise control over their structure and functionality. However, factors such as incomplete reactions and solvolysis can impact dendrimer synthesis, necessitating careful characterization using a variety of analytical techniques.

In terms of biomedical applications, dendrimers have shown promise in gene delivery, intracellular drug delivery, and as nanoscale containers for bioactive substances. Their ability to extravasate across microvascular endothelium further enhances their potential for targeted drug delivery and diagnostic imaging.

In summary, dendrimers represent versatile and adaptable nanocarriers with significant implications for drug delivery, diagnostics, and therapeutics. Continued research efforts aimed at elucidating their biological behavior and optimizing their synthesis and functionalization will pave the way for their widespread application in medicine and biotechnology.

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