IJMPR 2022, 6(10), 32-41

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

A RECENT REVIEW ON DENDRIMERS: SYNTHETIC STRATEGIES, TYPES, CHARACTERIZATION, PROPERTIES AND APPLICATIONS

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Received on: 03/09/2022
Revised on: 23/09/2022
Accepted on: 13/10/2022

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ABSTRACT
Dendrimers are a new class of polymeric materials. Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell. Their three traditional macromolecular architectural classes are broadly recognized to generate rather polydisperse products of different molecular weights. A variety of dendrimers exist, and each has biological properties such as polyvalency, self-assembling, electrostatic interactions, chemical stability, low cytotoxicity and solubility. Structural advantages allow dendrimers to play an important role in the fields of nanotechnology, pharmaceutical and medicinal chemistry. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached that is conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. The review aims to emphasize on construction, characterization, drug delivery and possible application of dendrimers in various areas of research, technology and treatment.

KEYWORDS: Dendrimers, Nanoscale, Monodisperse structure, Nanotechnology, Applications.

INTRODUCTION

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure consisting of tree-like arms or branches.[1] These hyperbranched molecules were first discovered by Fritz Vogtle in 1978, by Donald Tomalia and co-workers in the early 1980s, and at the same time, but independently by George R. Newkome. The second group called synthesized macromolecules 'arborols' means, in Latin, 'trees'. Dendrimers might also be called 'cascade molecules', but this term is not as much established as 'dendrimers'.[2-4] Dendrimers are nearly monodisperse macromolecules that contain symmetric branching units built around a small molecule or a linear polymer core.[5-7] 'Dendrimer' is only an architectural motif and not a compound. Polyionic dendrimers do not have a persistent shape and may undergo changes in size, shape, and flexibility as a function of increasing generations.[8-10] Dendrimers are hyperbranched macromolecules with a carefully tailored architecture, the end-groups (i.e., the groups reaching the outer periphery), which can be functionalized, thus modifying their physicochemical or biological properties.[11-16] Dendrimers have gained a broad range of applications in supramolecular chemistry, particularly in host-guest reactions and self-assembly processes. Dendrimers are characterized by special features that make them promising candidates for a lot of applications. Dendrimers are highly defined artificial macromolecules, which are characterized by a combination of a high number of functional groups and a compact molecular structure.[17] The emerging role of dendritic macromolecules for anticancer therapies and diagnostic imaging is remarkable. The advantages of these well-defined materials make them the newest class of macromolecular nanoscale delivery devices.[18] Dendritic macromolecules tend to linearly increase in diameter and adopt a more globular shape with increasing dendrimer generation. Therefore, dendrimers have become an ideal delivery vehicle candidate for explicit study of the effects of polymer size, charge, and composition on biologically relevant properties such as lipid bilayer interactions, cytotoxicity, internalization, blood plasma retention time, biodistribution, and filtration[19] (Figure 1).

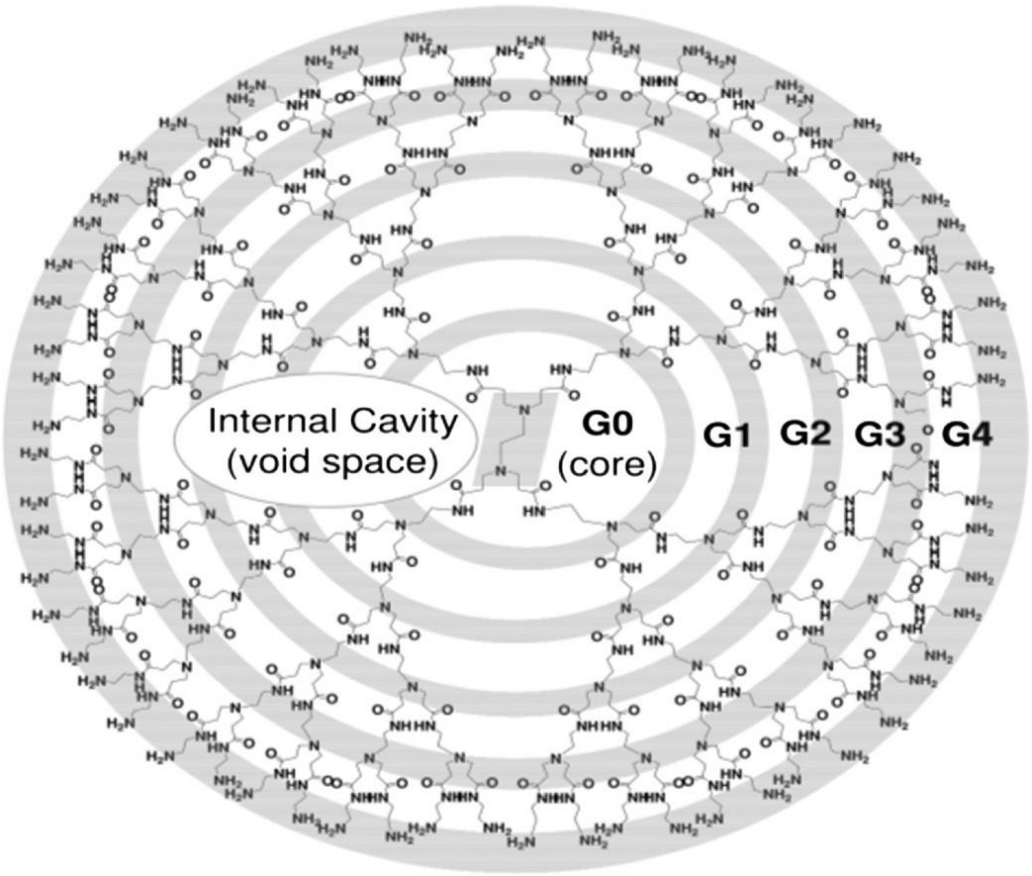


Figure 1: Schematic representation of a generation G4 dendrimer with 64 amino groups at the periphery. This dendrimer starts from an ethylene diamine core; the branches or arms were attached by exhaustive Michael addition to methyl acrylate followed by exhaustive aminolysis of the resulting methyl ester using ethylene diamine.[20]

History of Dendrimer

Dendrimers are an attractive exclusive class of polymers with controlled structure. A dendrimer is both a covalently assemble molecule and also a distinct nanoparticle. The first dendrimers be completed by divergent synthesis advanced by Fritz Vogtle in 1978, R.G. Denkewalter at AlliedCorporation in 1981, Donald Tomalia at Dow Chemical in 1983 and in 1985 and by George Newkome in 1985. In 1990 a convergent synthetic approach was introduce by Jean Fréchet. A lot of research has already been completed by studying the different properties and application of dendrimers but a lot of researchers still believe it to be in its initial stages.[21]

Structure and Chemistry

The structure of dendrimer molecules begins with a central atom or group of atoms labeled as the core. From this central structure, the branches of other atoms called 'dendrons' grow through a variety of chemical reactions. There continues to be a debate about the exact structure of dendrimers, in particular whether they are fully extended with maximum density at the surface or whether the end-groups fold back into a densely packed interior.[22,23] Dendrimers can be prepared with a level of control not attainable with most linear polymers, leading to nearly monodisperse, globular macromolecules with a large number of peripheral groups as seen in Figure 2, the structure of some dendrimer repeat units, for example, the 1,3-diphenylacetylene unit developed by Moore.[24] Dendrimers are a new class of polymeric belongings. Their chemistry is one of the most attractive and hastily growing areas of new chemistry.[26-28] Dendrimer chemistry, as other specialized research fields, has its own terms and abbreviations. Furthermore, a more brief structural nomenclature is applied to describe the different chemical events taking place at the dendrimer surface. Dendrigrafts are a class of dendritic polymers like dendrimers that can be constructed with a well defined molecular structure, i.e., being monodisperse.[29] The unique structure of dendrimers provides special opportunities for host-guest chemistry (Figure 3) and is especially well equipped to engage in multivalent interactions. At the same time, one of the first proposed applications of dendrimers was as container compounds, wherein small substrates are bound within the internal voids of the dendrimer.[30] Experimental evidence for unimolecular micelle properties was established many years ago both in hyperbranched polymers[31] and dendrimers.[32]

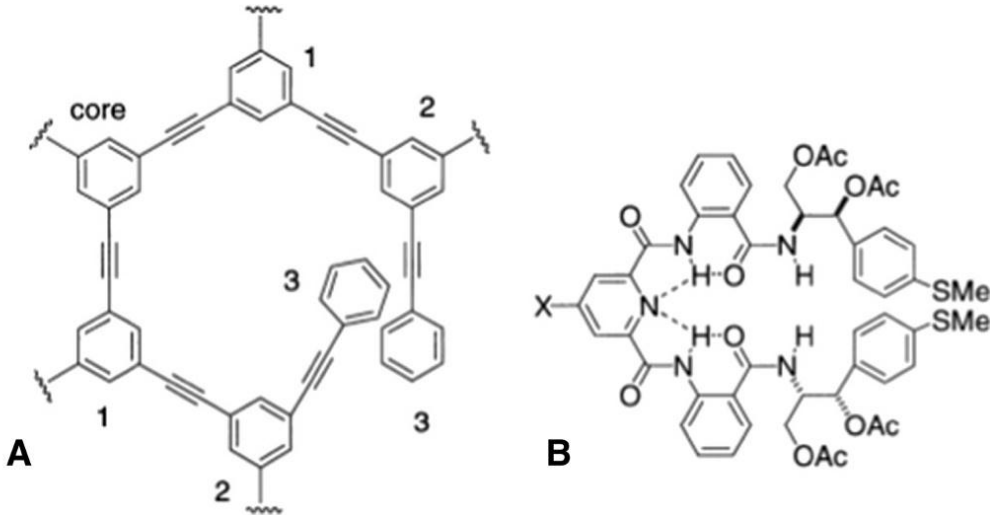


Figure 2: Types of dendrimers. (A) More type dendrimers consisting of phenyl acetylene subunits at the third-generation different arms may dwell in the same space, and the fourth-generation layer potential overlaps with the second-generation layer. (B) Parquette-type dendrons are chiral, non-racemic, and with intramolecular folding driven by hydrogen bonding.[25]

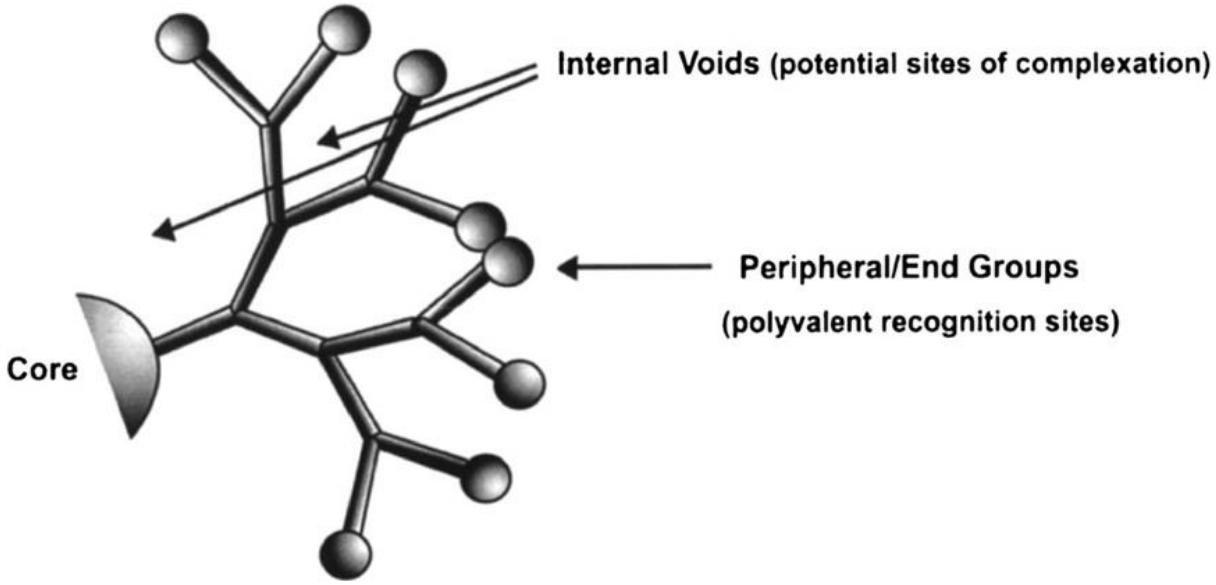


Figure 3: Three main parts of a dendrimer: the core, end-groups, and subunits linking the two molecules.

Advantages of Dendrimers

Dendrimers offers various advantages over other polymers.

- Dendrimers have nanoscopic particle size range from 1 to 100 nm, which makes them less susceptible for RES uptake.
- Due to stringent control during synthesis, they have lower polydispersity index. As the density of branches increases the outer most branches arrange themselves in the form of spheres surrounding a lower density core and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.
- Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body.
- Dendrimers can be modified as stimuli responsive to release drug.
- Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectively than small molecules.
- The advantage of dendrimers is that they can be synthesized and designed for specific applications. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.
- Medication to the affected part inside a patient's body directly.
- In target drug delivery: Dendrimers are suitable for targeting solid tumours due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumour (enhanced permeation rate). There is also

reduction in amount of drug multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components.[33-35]

Synthesitic Routes

Dendrimers are generated by changing functionality in each of their constituent parts (core, inner shell and periphery) to index properties such as solubility, thermal stability and addition of compounds for particular applications. Dendrimers are assembled from multifunctional core which is extended outward by a series of reactions called Michael addition reactions.[36] Each step of the reaction must be driven to conclusion in order to prevent trailing generations (some branches becoming shorter than others). The presence of trailing generations (impurities) can create negative impacts on the symmetry and functionality of the dendrimer, besides dendrimers are very difficult to purify because the relative size difference between perfect and imperfect dendrimers is diminutive. It is also a known fact that synthetic procedure can be applied to manage the size and number of branches on a dendrimer. There are two established methods for dendrimer synthesis, divergent and convergent synthesis, the choice of method for synthesis depends greatly on the target end application.

Divergent dendrimer synthesis

In the very early years of dendrimers, the synthetic approach to produce the two major dendrimers (PPI and PAMAM) relied on a step by step divergent strategy. Here the creation of the dendrimer takes place in a stepwise manner which begins from the core, followed by the build- up of the molecule towards the periphery using two basic operations namely; coupling of the monomer and secondly transformation of the monomer end-group to create a new reactive surface for the coupling of a new monomer. These two steps can be repeated several times to form different generations (tiers) of dendrimers with each generation having arms from previous generations.[37] This divergent rout for dendrimer synthesis is believed to be advantageous and very useful for commercial scale production because of high yield but with low purity. Impurities are encountered in the divergent synthesis of dendrimer as a result of either of the following side reactions missing repeating units, intra molecular/intermolecular cyclization or retro-Michael addition.

Convergent dendrimer synthesis

This method of dendrimer synthesis constructs a dendrimer from its surface and inwards towards the core via a one to one coupling of monomers thereby creating dendritic segments of increasing sizes as the synthesis progresses. During convergent synthesis of dendrimers the number of reactive sites found during the proliferation stage is usually minimal and this results to faster reaction rates with better yields. There is a large molecular difference between reactant molecules and products and this in turn facilitates the separation of products from reactants duringpurification. The convergent route of dendrimer synthesis is a practical means of producing dendrimers with mixed structural features because different segments are coupled together to generate dendrimers that posses heterogeneous morphologies.[38] The creation of dendrimers with heterogeneous morphologies opens up the fascinating fields of incorporating multiple active sites in one dendrimer to develop macromolecules with multifunctional design. The convergent synthetic route for dendrimer synthesis has been used for the synthesis of a wide range of dendrimers bearing different core functionalities, where the core is introduced at the last step of synthesis.[39] Therefore this methodology has facilitated the development of dendrimers with different core functions. Additionally, dendrimers synthesized by this route have less impurity with more monodispersity and symmetry because better purification is achieved before dendrons are finally attached to the core. However, the size of dendrimers synthesized via this route has limitations due to stearic hindrance between dendrons trying to get attached to the core.

Properties of Dendrimer

Some of the most important properties of dendrimers and linear polymer like structure, shape, structural control, architecture etc shown in the table 1.

Table 1: Properties of dendrimer and linear compact.[40]

S no.	Property	Dendrimer	Linear polymer
1.	Structure	Compact, Globular	Not compact
2.	Synthesis	Careful & stepwise growth	Single step polycondensation
3.	Structural control	Very high	Low
4.	Architecture	Regular	Irregular
5.	Shape	Spherical	Random coil
6.	Crystallinity	Non–crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials - Higherglass temperatures
7.	Aqueous solubility	High	Low
8.	Non-polar solubility	High	Low
9.	Viscosity	Non-linear relationship with molecularweight	Linear relation with molecular weight
10.	Polydispersity	Monodisperse	Polydisperse

Classification of Dendrimer

Dendrimer can be classification on the basis of their shape, structure, branching, solubility, chirality and attachment,which can be classified in table 2.

Table 2: Classification of dendrimers.[41]

S. No.	Classification of dendrimers	Application/Method
1	Simple Dendrimer	They have simple monomer units. The convergent synthesis of a sequence of monodisperse arelester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 and 46 benzene rings linked symmetrically and have molecular diameters of 45 A.
2	Liquid crystalline dendrimer	These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer. Functionalization to the end group of carbosilane dendrimers with 36 mesogenic units which can be attached through a C-5 spacer, and leads to liquid crystalline dendrimers that form broad smectic phase in the temperature range of 17°C to 130°C.
3	Chiral dendrimer	In chiral dendrimers the chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core e.g. chiral dendrimers obtained from pentaerythritol.
4	Micellar dendrimer	These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a collection of aromatic polymeric chain which able to generate an environment that resembles some micellar structures, which forms complex with small organicmolecules in water.
5	Hybrid dendrimer	These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. Which provide an opening to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers.
6	Amphiphilic dendrimer	These are the class of globular dendrimers that have asymmetrical but highly controlled division of chain end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion.
7	Metallo dendrimer	Dendrimers attached with the metal ion to form the complexation either in the interior or on the peripheral, which may be regarded as metallodendrimers. The ruthenium bipyridine complex based dendrimer have attribute electrochemical and luminescence properties.

Types of Dendrimers

Dendrimer can be differentiated on the basis of their shape, end functional groups and internal cavities, which can beclassified in table 3.

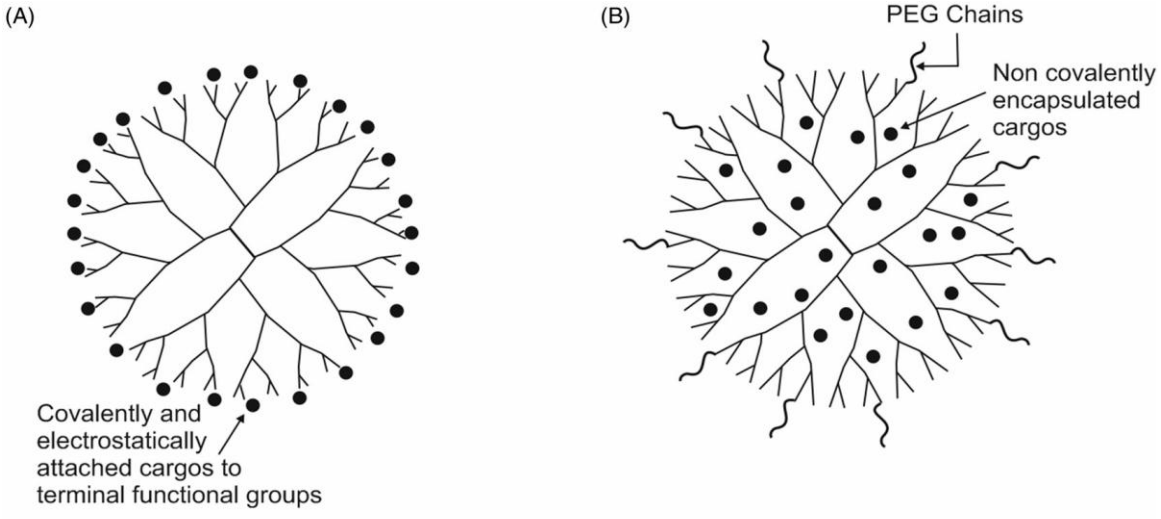
Table 3: Types of dendrimers.[42]

S No.	Types of Dendrimer	Synthesis	Examples	Identification
1	PAMAM (Poly Arnido Amine) Dendrimer	Divergent	Dendritech^{TM} (USA)	These are spheroidal or ellipsoidal in shape. It has high solubility and reactivity due to incidence of a number of functional end groups and empty internal cavities.
2	PPI (Poly Propylene Imine) Dendrimer	Divergent	Asramol by DSM (Netherlands)	Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as center. These are commercially available up to G-5 and are extensively used in material science and biology.
3	Chiral Dendrimer	Convergent	chiral dendrimers derived fromPentaerythritol	The chirality of the dendrimers was based upon the building ofconstitutionally different but chemically alike branches to chiral core.
4	Multilingual Dendrimers	Convergent	VivaGel	These are the dendrimers which hold multiple copies of a particular functional group on their surface.
5	Tecto Dendrimers	Divergent	Stratus® CS Acute Care^{TM}, Starburst®, Mercapto	These were made up of core dendrimers, which can be surrounded by other dendrimers, which execute a specific function leading to a smart therapeutic system used for diagnose the diseased state and deliver API to the accepted diseased cell.
6	Hybrid	Divergent	Hybrid dendritic linear	These dendrimers have characteristic of both dendritic and

	Dendrimers		polymer, Polysilsesquioxanes	linear polymer.
7	Amphiphilic Dendrimers	Divergent	SuperFetch,Hydra amphiphiles andbola-amphiphiles	These have one half that is electron donating and another halfis electron retreating.
8	Peptide Dendrimers	Convergent	Beta Casomorphin (human)	Peptide dendrimers are those which hold amino acid as branching or interior unit. These are used for the diagnostic purpose and vaccine delivery.
9	Frechet-Type Dendrimers	Convergent	Frechettype dendronazides, ™Priostar	These were based on polybenzyl etherhyper branched skeleton. Carboxylic acid group attached on the surface of dendrimers that provides site for further functionalization and also improve the solubility of dendrimers.
10	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergent	SARSOX	These are silicon containing commercial dendrimers which are inverted unimolecular micelles and contains exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamine.
11	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	vaccine and diagnostic research	These are dendron-like molecular assembly based upon apolylysine frame. Lysine with its alkyl amino side-chain performed as a excellent monomer for the overture of frequentbranching points.

Mechanisms of Action of Dendrimers

Dendrimers having positively charged surface groups, generally act to destabilize cell membranes and promote cell lysis by their membrane penetrations, while higher generation dendrimers show more toxicity based on their degree of substitution and type of amine functionality where primary amines show more toxicity compared to secondary or tertiary amines. PAMAM dendrimers having highly branched structures associated with large surface functional architectures, show greater activities to organisms enabling higher affinities and specific bindings to the cell receptors. The quaternary ammonium functional groups having high density to the dendrimers-surfaces show their antimicrobial activities implicating the annihilation of the microorganisms' cell membranes and multivalent linkages- disruptions between the microorganisms and the host cells which indicate the main antimicrobial mechanisms of the dendrimer biocides. The other dendrimeric primary surface functional binding groups are the hydroxyl, carboxyl, and amine, while amine groups of the PAMAM dendrimers show increased cytotoxic profiles, but hydroxyl and carboxylic- terminated groups less toxicity and more biocompatibility. These functional groups facilitate the conjugations of antimicrobial agents to the dendrimeric nanostructures surfaces[43] (Figure 4).



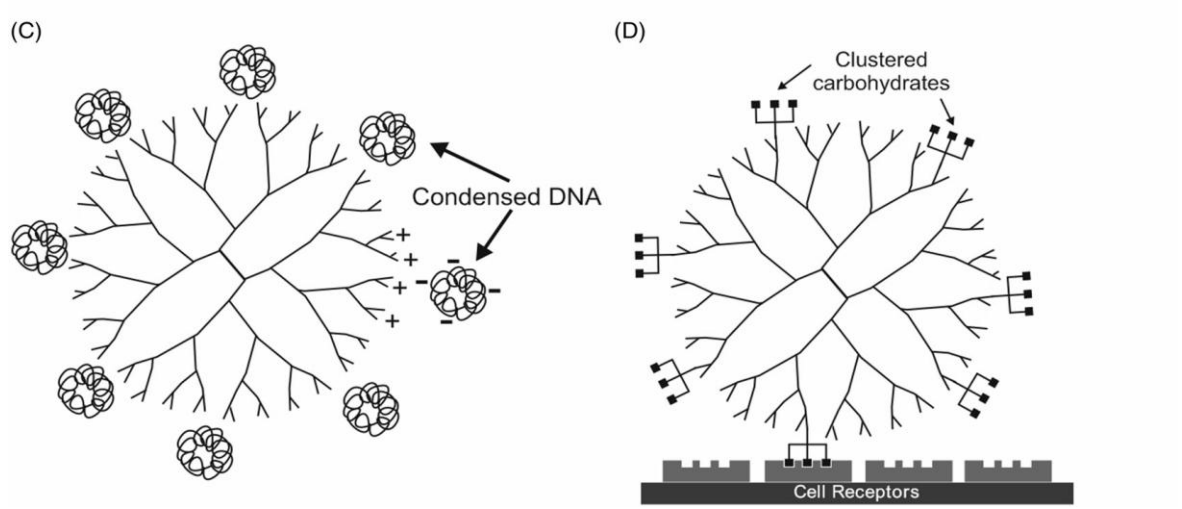


Figure 4: Electrostatic/covalent attachments of cargos to the periphery of dendrimer (A), whereas encapsulation of drugs in the interior cavities of dendrimer and functionalization by PEG (B). DNA may be conjugated to the positively charged PAMAM terminal groups (C). The functionalization of the amine groups of PAMAM with folates and carbohydrates may also be performed for cell-specific targeting (D).

Applications

Today, dendrimers have several medicinal and practical applications.[44]

Dendrimers in biomedical field

Dendritic polymers have advantage in biomedical applications. These dendritic polymers are analogous to protein, enzymes, and viruses, and are easily functionalized. Dendrimers and other molecules can either be attached to the periphery or can be encapsulated in their interior voids. Modern medicine uses a variety of this material as potential blood substitutes, e.g., polyamidoamine dendrimers.

Anticancer drugs

Perhaps the most promising potential of dendrimers is in their possibility to perform controlled and specified drug delivery, which regards the topic of nanomedicine. One of the most fundamental problems that are set toward modern medicine is to improve pharmacokinetic properties of drugs for cancer. Drugs conjugated with polymers are characterized by lengthened half-life, higher stability, water solubility, decreased immunogenicity, and antigenicity. Unique pathophysiological traits of tumors such as extensive angiogenesis resulting in hypervascularization, the increased permeability of tumor vasculature, and limited lymphatic drainage enable passive targeting, and as a result, selective accumulation of macromolecules in tumor tissue. This phenomenon is known as 'enhanced permeation and retention' (EPR). The drug-dendrimer conjugates show high solubility, reduced systemic toxicity, and selective accumulation in solid tumors. Different strategies have been proposed to enclose within the dendrimer structure drug molecules, genetic materials, targeting agents, and dyes either by encapsulation, complexation, or conjugation.

Dendrimers in drug delivery

In 1982, Maciejewski proposed, for the first time, the utilization of these highly branched molecules as molecular containers. Host-guest properties of dendritic polymers are currently under scientific investigation and have gained crucial position in the field of supramolecular chemistry. Host-guest chemistry is based on the reaction of binding of a substrate molecule (guest) to a receptor molecule (host).

Transdermal drug delivery

Clinical use of NSAIDs is limited due to adverse reactions such as GI side effects and renal side effects when given orally. Transdermal drug delivery overcomes these bad effects and also maintains therapeutic blood level for longer period of time. Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. Dendrimers have found applications in transdermal drug delivery systems. Generally, in bioactive drugs having hydrophobic moieties in their structure and low water solubility, dendrimers are a good choice in the field of efficient delivery system.

Gene delivery

The primary promise that the combination of understanding molecular pathways of disease and the complete human genome sequence would yield safer and more efficient medicines and revolutionize the way we treat patients has not been fulfilled to date. However, there is little doubt that genetic therapies will make a significant contribution to our therapeutic armamentarium once some of the key challenges, such as specific and efficient delivery, have been solved. The ability to deliver pieces of DNA to the required parts of a cell includes many challenges. Current research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the

dendrimer/ DNA complexes were encapsulated in a water soluble polymer and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substrate-mediated gene delivery. Research has shown that the fast-degrading functional polymer has great potential for localized transfection.

Dendrimers as magnetic resonance imaging contrast agents

Dendrimer-based metal chelates act as magnetic resonance imaging contrast agents. Dendrimers are extremely appropriate and used as image contrast media because of their properties.

Dendritic sensors

Dendrimers, although are single molecules, can contain high numbers of functional groups on their surfaces. This makes them striking for applications where the covalent connection or close proximity of a high number of species is important. Balzani and coworkers investigated the fluorescence of a fourth-generation poly (propylene amine) dendrimer decorated with 32 dansyl units at the periphery. Since the dendrimer contains 30 aliphatic amine units in the interior, suitable metal ions are able to coordinate. It was observed that when a Co2+ ion is incorporated into the dendrimer, the strong fluorescence of all the dansyl units is quenched. Low concentrations of Co^{2+}ions (4.6×10^{-7}M) can be detected using a dendrimer concentration of 4.6×10^{-6}M. The many fluorescent groups on the surface serve to amplify the sensitivity of the dendrimer as a sensor.

Dendrimers used for enhancing solubility

PAMAM dendrimers are expected to have potential applications in enhancing solubility for drug delivery systems. Dendrimers have hydrophilic exteriors and interiors, which are responsible for its unimolecular micelle nature. Dendrimer-based carriers offer the opportunity to enhance the oral bioavailability of problematic drugs. Thus, dendrimer nano carriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

Photodynamic therapy

Photodynamic therapy (PDT) relies on the activation of a photosensitizing agent with visible or near-infrared (NIR) light. Upon excitation, a highly energetic state is formed which, upon reaction with oxygen, affords a highly reactive singlet oxygen capable of inducing necrosis and apoptosis in tumor cells. Dendritic delivery of PDT agents has been investigated within the last few years in order to improve upon tumor selectivity, retention, and pharmacokinetics.

Miscellaneous dendrimer applications

Clearly, there are many other areas of biological chemistry where application of dendrimer systems may be helpful. Cellular delivery using carrier dendritic polymers is used in the purification of water dendrimer-based product in cosmetics contaminated by toxic metal ion and inorganic solute, and dendrimer-based commercial products organic solutes. Furthermore, highly sensitive analytical devices, MRI contrast agents, prion research, burn treatment and EPR imaging with spin-labeled dendrimers are some of the diverse areas of fascinating ongoing dendrimer research that are beyond the scope of this article.

Characterizations of Dendrimeric Composites

The dendrimers are characterized by different instrumental analysis. The morphology of the dendritic nanoparticles may be analyzed by atomic absorption, scanning electron or transmission electron microscopies. The particle size and zeta potential of dendrimeric composites may be determined by dynamic light scattering analyzer. The synthesis, chemical transformation, molecular interaction, chemical ionization, quantification, and chemical composition, size, shape, and structure of dendrimeric composites may be determined by ultraviolet-visible spectroscopy, infrared spectroscopy, near infrared spectroscopy, mass spectroscopy, fluorescence and X-ray diffraction analysis, respectively. The partition of dendrimeric molecules according to size may be determined by size exclusive chromatography, whereas the quantitative determination of the effective dendrimeric substitutions on their surfaces by electron paramagnetic resonance. The synthesized transition temperature, complete information about molecular dynamic processes and the detailed information about chemical compositions of dendrimeric composites on layers may be actuated by differential scanning calorimetry, dielectric and X-ray photoelectron spectroscopies, respectively.[43]

Conclusions and Future Perspectives

Dendrimeric delivery systems are attracting interest in delivering many bioactive compounds to diseased sites. However, potential positively surface-charged higher generated dendrimers having primary amines, exhibit their high toxicities to cells.[45] To reduce the cytotoxicity, the synthesis and polymerization of the dendrimers may be controlled and their surfaces may be functionalized/encapsulated with different biological ingredients/copolymers such as sugars, proteins, peptides, genes and other targeting agents/PEG into their hollow branching voids utilizing electrostatic and covalent bindings/encapsulation for enhancing the solubility, stability and the sustained release of the cargos as passive or receptor-mediated active targeting to the affected cells. As dendrimers are hyperbranched, it has been emphasized to develop dendrimeric clusters for assembling a multifunctional therapeutic system in incorporating different cargos, targeting ligands or other agents for effective delivery to targeted cells and to

overcome the biological barriers. However, a thorough and systemetic investigation regarding biodistribution, pharmacokinetics, biodegradation, elimination and chronic toxicity of dendrimeric nanoparticles in different in vivo administrative routes, mainly intravenous and oral, is required before going to clinics for proper clinical applications.

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