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A Review Article On: Amphiphilic Dendrimers And Their Biomedical Uses

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INTRODUCTION

Dendrimers are highly branched polymers with easily modifiable surfaces. This makes them promising structures for functionalization and also for conjugation with drugs and DNA/RNA. Their architecture, which can be controlled by different synthesis processes, allows the control of characteristics such as shape, size, charge, and solubility. Dendrimers have the ability to increase the solubility and bioavailability of hydrophobic drugs. The drugs can be entrapped in the intramolecular cavity of the dendrimers or conjugated to their functional groups at their surface. Nucleic acids usually form complexes with the positively charged surface of most cationic dendrimers and this approach has been extensively employed. The presence of functional groups in the dendrimer's exterior also permits the addition of other moieties that can actively target certain diseases and improve delivery, for instance, with folate and antibodies, now widely used as tumor targeting strategies. Dendrimers have been investigated extensively in the medical field, and cancer treatment is one of the greatest areas where they have been most used.There are two significant advantages using dendrimers as the template for the nanoparticle/cluster synthesis. One is the precise and flexible control of the particle size. This advantage is brought by the preorganization of precursor molecules in the dendrimer template that can be preprogramed by the stoichiometry. Another advantage is the precise synthesis of multimetallic nanoparticle/cluster reducing the uncertainty of the bimetallic composition. From the standpoint of catalysis, the dendrimer route also allows the application even in homogeneous catalysis because a nanoparticle in a dendrimer.

Dendrimers have a regular branched structure and spherical shape. Characteristic surface groups with hydrophobic or hydrophilic components can encapsulate ligands inside or attach them to the surface, ensuring protection against degradation. Drug molecule complexed with dendrimer can be delivered to target cells and then released from the complex. Dendrimers can improve the bioavailability of drugs by increasing their solubility in water, changing of surface charge, and by reducing toxicity. Dendrimers can effectively transfect many kinds of biomolecules, such as proteins, peptides, enzymes, gene material and others, to the target cells

There are many reports describing those dendrimers are more efficient than viral vectors, liposomes and linear polymers in delivering different kinds of biomolecules

Dendrimers, as a type of artificial polymers with unique structural features, have been extensively explored for their applications in biomedical fields, especially in drug delivery. Dendrimers are a family of synthetic polymers with three-dimensional, highly branched and well-defined architectures. The term dendrimer was derived from the Greek words "Dendron" meaning "tree", which gave a vivid description of their distinctive "tree-like" branched structure.Dendrimers are highly branched monodisperse macromolecules with a well-defined structure. The main difference between dendrimers and other nanoscale molecules is the possibility to control their chemical composition, size, and architecture. It allows designing structures with unique properties for various applications.Dendrimers have a 3D branched topology with special physical and chemical properties, a well-defined globular shape, multifunctionalities, and potential application as materials, catalysts, and in biology Dendrimers are tree-like synthetic macromolecules with a large number of branching points, a 3D globular architecture, monodispersity, and a nanolevel size. In this well-defined structure, terminal units are on the globular surface and the dendritic units are internal. Diverse applications of dendrimers are possible because such macromolecules serve as carriers for both hydrophilic and hydrophobic drugs or nutrients and can deliver them to a specific target.

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The layers from the central core of a dendrimer resemble the layers of an onion and are often known as 'generations. Based on the number of generations, the effects of a dendrimer can be negative or positive. However, most negative results are not published. Dendrimer effects are positive up to a certain number of generations and are negative thereafterDendrimers with up to six generations can efficiently penetrate cells, whereas the rate of penetration decreases in dendrimers with six to ten generations.

1.1. TYPES OF DENDRIMERS

The first synthesized dendrimers were polyamidoamines (PAMAMs) introduced in 1980s; however, various other dendrimers including poly(propylene imine) dendrimers (PPI), tecto dendrimer, and amphiphilic dendrimers, were synthesized in the later years (Alper, 1991). PAMAM dendrimers are also called as "Starburst®" dendrimers, a trademark of the Dow Chemicals Company. The term "dendrimer" comes from the word "Dendron," which means a tree. Newkome's group independently reported synthesis of analogous macromolecules, and termed those as "arborols," which is derived from a Latin word "arbor," which again means a tree. Another term used for this highly branched polymer structure is "cascade molecule." Although these hyper-branched molecules have multiple names, "dendrimer" is the most commonly used term

Dendrimer is a synthesized, multi-branched polymeric composition where the branches of the polymer originate from the core. Unique characteristics of dendrimers include their uniformly dispersed design, relatively spherical shape, adaptable surface composition, multi-valency, aqueous-solubility, and available hydrophobic pockets/cavities at the interior which can encapsulate hydrophobes. PAMAM are the most widely used dendrimers. Dendrimer can be easily tailored at the surface as well as at the interior layers which makes it a versatile host for encapsulation, complexation, conjugation and finally the delivery of a variety of therapeutic molecules. Dendrimers are prepared by a repetitive synthesis process which correspondingly increases the generations and determines the physico-chemical characteristics of the dendrimer product. Dendrimers are unique hyper-branched material with great versatility. They differ from conventional linear natured polymers in that dendrimers have compact and globular structure which is not compressible, and have a spherical shape in contrast to the non-compact, compressible and irregular architecture of linear polymers. A comparison between linear and hyper-branched polymer is summarized in Table 1. In general, lower generation dendrimers possess open structure, and become globular, compact and dense with increasing generations. Moreover, dendrimers are found to be analogous to some biological structures; for example, insulin, cytochrome C, hemoglobin, prealbumin, and hemerythrin closely match with ammonia core PAMAM G3 (3.1 nm in diameter), G4 (4 nm), G5 (5.3 nm), G6 (6.7 nm), and G7 (8 nm) dendrimers, respectively, in terms of dimensional size and the shape.

The use of nanotechnology in biology and medicine has been marked by rapid progress of these industries due to the emergence of new devices, supramolecular systems, structures, complexes and composites. One striking example of nanotech polymers is dendrimers. Their structure is formed by branches of monomeric subunits diverging in all directions from the central core. In choosing monomers and functional groups in synthesis, one can precisely set the properties of the resulting macromolecules. Currently, with modifications, >100 types of dendrimers have been synthesized. Of these, the 5 most common families can be distinguished: (i) Polyamidoamine (PAMAM) dendrimers are based on the ethylenediamine core and their branches are constructed from methyl acrylate and ethylene diamine. Currently, there is a large selection of PAMAM dendrimers with surface groups of many types. (ii) Polypropyleneimine (PPI) dendrimers are based on a butylenediamine core and polypropyleneimine monomers. In addition to PPI, the second popular abbreviation of these dendrimers is DAB (diaminobutyl) – from the name of the nucleus. Currently commercially available are (iii) Phosphorus dendrimers. In phosphorus dendrimers, phosphorus atoms are present in the core and branches of the dendrimer. (iv) Carbosilane dendrimers are based on a silicon core and have ammonium or amino groups on the periphery. (v) Poly(lysine) and poly(L-ornithine) dendrimers are a dendrimeric structure composed of amino acids residues. Characteristic surface groups possessing hydrophobic or hydrophilic components help to encapsulate the ligands inside or attach them to the surface, ensuring protection from degradation. Drug molecules complexed with dendrimer can be delivered to target cell where they are released from the complex. Dendrimers can improve the bioavailability of drugs by increasing their solubility in water, and changing surface charge, thereby reducing toxicity.

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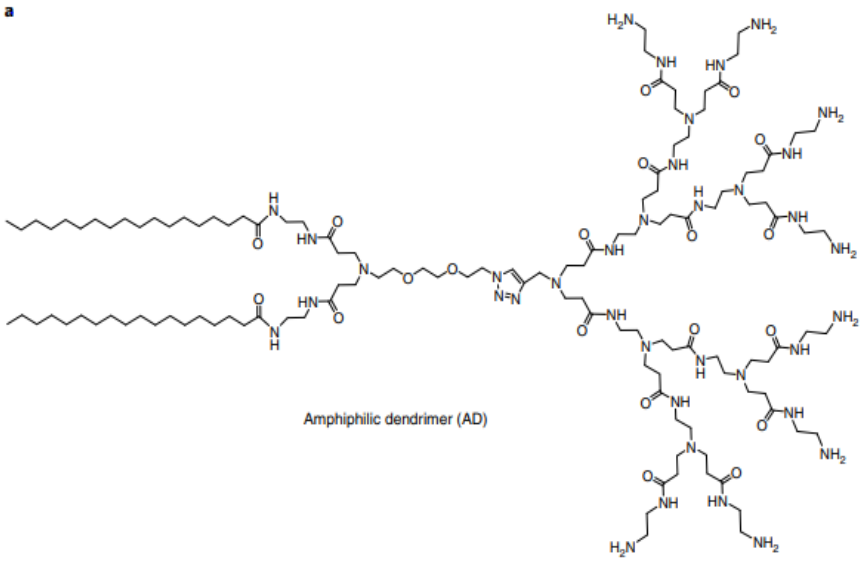
1.2. AMPHIPHILIC DENDRIMERS

In recent years, a new class of dendrimer, known as Janus dendrimers (JDs), has attracted much attention due to their different structures and properties to the conventional symmetric forms. The broken symmetry of JDs offers the opportunity to form complex self-assembled materials, and presents new sets of properties that are presently inconceivable for homogeneous or symmetrical dendrimers. Due to their unique features, JDs have a promising future in pharmaceutical and biomedical fields, as seen from the recent interest in their application in conjugating multiple drugs and targeting moieties, forming supramolecular hydrogels, enabling micellar delivery systems, and preparing nano-vesicles, known as dendrimersomes, for drug encapsulation. The present paper is the first review, with an emphasis on various emerging applications of JDs, in the drug delivery and biomedical field reported so far. In addition, the paper describes different synthetic methods for producing JDs that can guide the design of new biocompatible forms with pharmacological activities, and that have the potential to be nano drug delivery vehicles. Furthermore, future studies to optimize the applications of JDs in drug delivery sciences and biomedical field to realize their potential to treat various disease conditions are identified and highlighted. Overall, this review identifies the current status of JDs in terms of their synthesis and applications, as well as the future research for their translation into macromolecules for clinical applications to solve health problems. It highlights the future combined efforts needed to be taken by dendrimer chemists, formulation scientist and microbiologists to develop novel antibacterials and nanomedicines from JDs.[22] Amphiphilic dendrimers, constructed from long hydrophobic alkyl chains and PAMAM dendrons, have emerged as newcomers in the drug delivery field. These amphiphilic dendrimers are able to capitalize on the delivery features of lipid and polymer vectors while minimizing adverse toxic effects [23-25] They can assemble into supramolecular nanostructures and can be loaded with therapeutic cargos, either through hydrophobic encapsulation within the interior of a dendrimer nanomicelle11 or via electrostatic interaction with the charged amine functionalities on the dendrimer surface.12−14 While these assemblies have proved highly effective compared to traditional lipid or dendrimer vectors, interest is growing around the coassembly of synthetic compounds with naturally occurring phospholipids for the assembled constructs' potential to demonstrate both natural and tunable biophysical properties. [26]Amphiphilic dendrimer-like polymers are expected to be promising candidates as micro containers or carriers due to their much larger size in relative to regular dendrimers. [27]



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Amphiphilic dendrimer dominantly formed hydrophobic modified-PPI cores surrounded by hydrophilic PAMAM dendrimer. Amphiphilic dendrimers, as an important branch of the dendrimer family, can be endowed with amphiphilic balance and unique aggregation behavior by introducing appropriate modifications. Amphiphilic bis-MPA derivatives- based dendrimers have been used in the application of biomedical field. Bis-MPA derivatives have shown a great therapeutic efficacy in drug delivery because of their ability to be degraded by enzymes, their compatibility, and high solubility in biological environments. They also consist of functional groups that make it easy to encapsulate antimalarial drugs shows a typical example of amphiphilic dendrimers.

1.2.1 Classification of Amphiphilic Dendrimers

Depending on the structural arrangement of hydrophilic and hydrophobic segments, amphiphilic dendrimers can be classified into [i] Amphiphilic Layered [ii] Amphiphilc Di-block or Janus, and [iii] Facially amphiphilic dendrimers

1.2.1.1. Amphiphilic Layered Dendrimers

Amphiphilic Layered dendrimers are also known as dendritic core shell and can be prepared by incorporating a contrasting block between different layers, i.e., with hydrophobic core and hydrophilic corona or vice versa. These types of Dendrimers were first synthesized by Newcome and co-workers in 1985 using a divergent technique through the functioning of the polar-ol corona on non-polar arborol core. As a result of the layered structural arrangements, these amphiphilic dendrimers were able to self-assemble to form unimolecular micelles that could encapsulate hydrophobic guest molecules and maintain their career function under high dilution. With the introduction of these dendrimers, unimolecular self-assembly attracted attention, as single molecule can perform micelles-like properties without aggregating with other molecules. These types of unimolecular self-assemblies can be stable to various in vivo environmental changes, such as concentration variation, interaction with lipids and proteins, and flow stress, which could lead to disaggregation and early drug release. Frechet and co-workers also reported the convergent synthesis of amphiphilic layered dendrimers with a 3,5-dihydroxybenzyl core and carboxylate end group at the periphery. These amphiphilic dendrimers were synthesized by the convergent method, where two polyether dendrons were grown convergently by using methyl p-bromomethyl benzoate as a starting material, which became a peripheral functional group with protected methyl esters. In the interior 3,5-Dihydroxylbenzeyl alcohol as monomeric units were coupled to the methyl p-bromomethyl benzoate as a starting material, which became a peripheral functional group with protected methyl esters. In the interior 3,5-Dihydroxybenzyl alcohol as monomeric units were coupled to the methyl p-bromomethyl benzoate. This was followed by a two step generation growth process that involves activation by bromination and propagation by alkylation. Furthermore, two protected polyether dendrons were coupled together with the bifunctional core, 4,4-Dihydroxybiphenyl, in the presence of K2CO3, after which the methyl ester groups were deprotected by alkaline hydrolysis to obtain hydrophilic carboxylate end groups (Hawker et al., 1993). Several other research groups later synthesized amphiphilic layered dendrimers, studied their self-assembly into unimolecular micelles and evaluated their capacity for encapsulating hydrophobic guest molecules.

1.2.1.2. Amphiphilic Diblock or Janus Dendrimers

Amphiphilic diblock Dendrimers can be prepared by covalently bonding two different types of dendrons in a single molecule. This functional arrangement provides hydrophilic and hydrophobic groups on the extreme end of the dendritic structure, which results in a broken symmetry with differing solubilities of the two contrasting regions. This offers new properties to form complexes of self-assembled structures, such as bilayer spherical assemblies that are known as dendrimers. Janus Dendrimers were first synthesized by Wooley and Frechet as unsymmetrically functionalized Dendrimers, with the non-polar benzyl and polar benzoate functional groups possessing large dipole moments. The Janus Amphiphilic Dendrimers could not form unimolecular micelles but acted as surfactants at oil-water interface and self-assembled into micellar aggregates. They can be synthesized by Three Synthetic methods: [i] Chemo selective Coupling, [ii] Heterogenous double exponential growth method, and [iii] Mixed Modular approach, details of which can be found elsewhere. It is envisaged that Janus Dendrimers could revolutionize the drug delivery field, as their diverse application are due to their unique characteristic features.

1.2.1.3. Facially Amphiphilic Dendrimers

Facially, Amphiphilic Dendrimers are comprised of repeating Amphiphilic monomeric

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unis that create uniform amphiphilicity over dendritic surface, thus polar and non-polar functionalities are distributed throughout the dendritic structure and also referred to as Amphiphilic Dendritic homopolymers. These Amphiphilic Dendrimers were first described by Thayumanvan and co-workers in 2004, where they synthesized AB2-functionalized facially Amphiphilic Dendrimers via a biaryl monomer composed of a carboxyl group as polar moiety, and dodecyl chain as the non-polar moiety.

1.2.2. Application in Drug Delivery

With advances in synthetic methodologies for Dendrimers, and with an increasing need by pharmaceutical scientists for controlled and targeted drug delivery, both stimuli and non-stimuli responsive Amphiphilic Dendrimers have been reported in the literature of drug delivery application. This section is divided into two major sections: non-Stimuli responsive self-assembling Dendrimers and stimuli responsive self-assembling Dendrimers. These major sections are both further divided into Three sub-sections: (i) Amphiphilic Layered, (ii) Janus, (iii) Facially Amphiphilic Dendrimers-based drug delivery system, depending on their classification. Finally, the section summarizes the application of low-molecular-weight dendritic amphiphiles in drug delivery.Dendritic macromolecules, due to their structure, unique properties, and precise compositions, are of significant interest and are finding uses in an ever-increasing number of medical applications.This is especially evident in the drug delivery area where the dendritic structure enables the attachment of a multitude of drugs or targeting moieties as well as the opportunity to control pharmacokinetics through alterations in generation number.Our interest lies in the synthesis and evaluation of dendritic macromolecules composed of building blocks that are natural metabolites or known to be biocompatible for ocular tissue repair, cartilage tissue engineering, and drug delivery. To expand the biomedical applications of dendrimers and our understandings ofthe resulting structure-activity relationships, we are investigating anionic dendritic macromolecules as antibacterial agents. Herein, we report the antibacterial activity of an anionic amphiphilic dendrimer and the striking selectivity in its cytotoxicity toward a prokaryotic Grampositive bacterium compared to a eukaryotic human cell. There is a significant global need for new antibacterials and alternative mechanisms of action given the rise in resistance among bacteria. of the various known antibacterial agent classes, amphiphilic compounds act through perturbation and disruption of the prokaryotic membrane.

Purpose	Description of JD system	Important findings	Major advantages of the conjugation system	Ref.
1. Stochastic approach	a) G1, G2, G3 Polyethylene oxide (PEO) dendrimers with terminal hydroxyl group & other side protected acetal group. Conjugated with camptothecin on one side & folic acid on the other b) Asymmetrical 2, 2-bisMPA based polyester dendrimers conjugated with Dox attached with pH responsive hydrazone linkages on one side and polyethylene oxide on the other.	• Stochastic approach with multi functionalization property. • Stability and solubility enhancement. • Targeted delivery. • Decreased toxicity. • Increased solubility. • pH-dependent release. • Increased uptake. • Increased antitumor activity.	Selective and sequential attachment of two different functional moieties on a single JD. Modulation of pharmacokinetic properties with enhanced antitumor activity by providing multiple functional handles to attach Dox and hydrophilic PEO.	(Feng et al., 2011) (Lee et al., 2006)
2. Multiple drug conjugation (Combination therapy)	PEG-based JDs conjugated with two different model drugs, viz., benzyl alcohol and 3-phenyl propionic acid attached via carbonate and ester linker respectively.	• Conjugation of two different classes of drugs precisely on a single JD. • Sequential drug release	Precise attachment of two drugs with different pharmacological actions having sequential release pattern & the ability to self-assemble in nano vesicular forms.	(Acton et al., 2013)
3. Solubility enhancement	Aspartic acid oligopeptides and naproxen based poly amido-ester JDs	• Enhanced water solubility of attached naproxen.	Synthesis of dendritic prodrugs with multiple solubilizing groups and bone-targeting oligopeptides	(Ouyang et al., 2010)
4. Lipophilization of antioxidants	JDs with multiple gallic acid moieties (as antioxidants) and multiple myristic acid as lipophilic moiety.	• Moderate enhancement of antioxidant activity • Increased lipophilicity. • This amphiphilic structure can be used as an antioxidant in oil based media.	Enhancing both antioxidant activity and lipophilicity of gallic acid using same dendritic scaffold	(Pan et al., 2013)
5. Targeted delivery	JDs with multiple polarized acidic amino acids (L-Asp or L-Glu) & nonpolar naproxen as a potential dendritic scaffold for bone targeted delivery	• Conjugated multiple acidic amino acids on dendritic display provided bone targeting ability to attached model drug, naproxen.	JDs showed the ability to carry multiple drug molecules and bone targeting molecules simultaneously.	(Pan et al., 2012b)
6. Fluorescent labels	JDs consists of ammonium terminal groups on one side and fluorescent dansyl derivative on other built with hexafunctional cyclotriphosphazene core.	• JDs with multiple cationic & fluorescent groups synthesized with a minimum numbers of steps using two routes. • All synthesized JDs have a bright fluorescence.	Water soluble fluorescent JDs with promising photophysical behaviors with the potential to be used as fluorescent labels in material science and biology.	(Fuchs et al., 2008)

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