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# A systematic review of polyamidoamine dendrimers about structure, characteristics, synthesis, structure modification and application.

Mengmeng Huo, Arka Sen Chaudhuri, Wenyan Li, Yuchao Fan, Xiu Han, Chen Yang, Zhenghong Wu, Xiaole Qi

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# A systematic review of polyamidoamine dendrimers about structure, characteristics, synthesis, structure modification and application

Mengmeng Huo, Arka Sen Chaudhuri, Wenyan Li, Yuchao Fan, Xiu Han, Chen Yang, Zhenghong Wu *, Xiaole Qi *

*Key Laboratory of Modern Chinese Medicines, China Pharmaceutical University, Nanjing 210009, P. R. China*

*Corresponding authors: Zhenghong Wu; Xiaole Qi

E-mail address: zhenghongwu66@cpu.edu.cn (Z. H. Wu); qixiaole523@163.com (X. L. Qi); Tel: +0086-15062208341; Fax: +0086-025-83179703

## Abstract

Polyamidoamine (PAMAM) dendrimers have received considerable attention in recent years due to their unique shape, small size and placement of functional groups. PAMAM dendrimers were the first complete dendrimer family to be synthesized, characterized and commercialized. And PAMAM dendrimers are good drug carriers for application in drug delivery and biomedical with high degree of uniformity, monodispersity and high density functional end groups. This review provides a brief description of PAMAM dendrimers and its applications. The structure and characteristics of dendrimers, the synthesis of dendritic architecture, the structure modification of dendrimers and the application of dendrimers were described. Overall, PAMAM is a promising carrier in drug delivery system with considerable potential.

## Keywords

Polyamidoamine dendrimers, structure and characteristics, synthesis, structure modification, application.

## Introduction

Dendrimers have received considerable attention in recent years due to their unique shape, small size and placement of functional groups that is desirable for many life science applications[1]. PAMAM dendrimers were the first complete dendrimer family to be synthesized, characterized and commercialized[2]. Tomalia and his co-workers synthesized Polyamidoamine (PAMAM) dendrimers in 1984 for the first time. PAMAM dendrimers with high degree of uniformity, monodispersity and high density functional end groups are reported good drug carriers for application in drug delivery and biomedical[3, 4]. However, we have to remember that there are also some disadvantages, which limit the use of PAMAM dendrimers such as high cytotoxicity and rapid clearance from the circulation after intravenous administration[5]. The toxicity of PAMAM dendrimers is a result of their intense surface positive charge under physiological conditions and nonselective interactions of PAMAM with both normal and tumor cells. After structure modification, PAMAM is a promising carrier in drug delivery system with considerable potential. This review provides a brief description about structure and characteristics of dendrimers, the synthesis of dendritic architecture, the structure modification of dendrimers and the application of dendrimers.

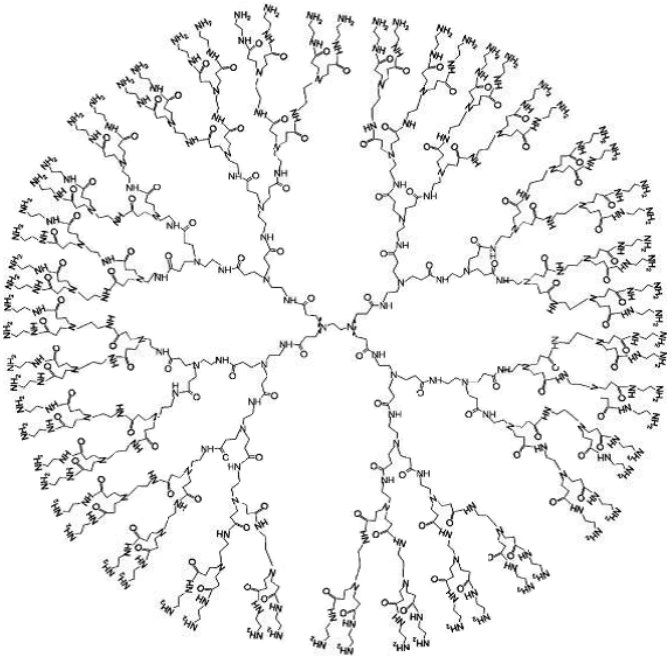

Figure 1 Structure of PAMAM

## **1.** Structure and characteristics of PAMAM

In 1985, Tomalia et al. first synthesized highly branched, symmetrical, radial polyamide-amine macromolecule[5], and called it a star-shaped dendrimer. The polyamide-amine dendrimer consists of three architectural structures, an initial core, a repeating branching unit that is radially connected to the initial core, and a terminal group attached to the outer repeating units.

The size of PAMAM dendrimers ranges from 1 to 20 nm diameter for generation 1 (G1) through generation 10 (G10) dendrimers. As the number of surface functional groups increases, the generation of PAMAM increased, and eventually leading to the changes of surface space and geometric. When the generation of polyamide-amine dendrimer is low, from G0 to G3 generation dendrimers, they have a planar, liner structure. PAMAM from G4 to G10 (higher generation dendrimers) have a spherical shape because their branches are densely packed. With the increase of outer surface, the generation increased by 1, and the current polyamide-amine dendrimers have been synthesized to 10 generation[6, 7]. Polyamide-amine has the following structural characteristics: (1) high-density surface functional groups; (2) a high degree of geometric symmetry; (3) spherical molecules; (4) initial cavity and adjustable; (5) structural regularity, molecular structure is accurate; (6) controllable molecular.

## **2.** Synthesis of PAMAM

There are two kinds of synthetic methods of dendrimers: one is divergent synthesis method, that is, the synthesis procedures from the inside to outside; the other synthetic method is the convergence, that is, from the outside to the inside.

### 2.1 divergent method

The divergent synthesis method is proposed by Vogtle et al., Using a synthetic process that progressively diffuses out from a center[8]. It is convenient to deploy functional groups in the periphery, but with the growth of generation, the functional groups of the reaction process are doubled, which leads to incomplete reaction and

structural defects in the molecule, so that the monodisperse of the structure can not be guaranteed. However, the defective product is similar to the target product in the structure and properties, and the inclusion of the macromolecule to the excess monomer, making the separation of the product very difficult. Thus, applicable reaction using the divergent method requires high requirements: the reaction must have a high conversion rate (> 90%) and the excess monomer is easy to remove.

2.2 Convergent growth process

The convergent growth synthesis method was proposed by Hawker and Fréchet in 1990[9], which is different from the divergent synthesis. In this method, a "wedge" structure, which is then connected to the core and finally forms a new dendritic macromolecule. This synthetic method is very clever, with the increase in the number of multiplication, the activity of each reaction does not increase, which is conducive to complete reaction, so that the end of the structure is complete. The disadvantage of the convergence method is that the growth of molecular weight is slow, the space barrier is very large when it is the synthesis of large structures, resulting in low yield. It need more raw reaction materials in order to achieve a certain yield. To obtain a dendrimer structure, several dendrons are reacted with a multi-functional core to yield such a product

2.3 divergent method and convergent growth process method

This method combined with the advantages of the above two methods, usually, first using the divergent method to form the hyper core of lower generation of PAMAM dendrimers, and then using the convergence method to obtain a certain generation monomer, and then the branched monomer is attached to the hyper core. Using both of the convergence method and the divergence convergence method, more than 100 compositionally different dendrimer families have been synthesized[10].

## 3. Structure modification of PAMAM

The surface of PAMAM has a large number of positively charged amino groups, which interact with the negatively charged cell membrane, causing apoptosis. However, highly positive surface charge always results in high cytotoxicity and rapid clearance by macrophages from the circulatory system. Therefore, We need to find some good ways to deal with this. According to to structure modification of PAMAM in the end groups, it is easy to reduce positive charges on PAMAM surface, reducing cytotoxicity make it a great drug carrier in drug delivery system researches. In this paper, a brief description about structure modification of PAMAM had been provided.

### 3.1 Polyethylene glycol modification

Polyethylene glycol (PEG) is a kind of non-toxic, water-soluble immune-inert macromolecular polymer, PAMAM can be modified by polyethylene glycol to reduce cytotoxicity and improve biocompatibility. PEG-modified PAMAM complexes have a water-soluble shell and insoluble core, resulting in a single molecule micelle, so PEG can improve the water solubility and biocompatibility of PAMAM[11].

Yang et al[12] synthesized 1-5 generation PAMAM macromolecules by divergent method and PEGylated PAMAM. The synthesized compounds were characterized by IR, NMR, end titration and GPC methods, then compared the drug loading and release effects of PAMAM and PEGylated PAMAM. The results of IR, NMR, end titration and GPC showed that the synthesized products 1-5 generation PAMAM dendrimers, and the results of IR were used to identified the PEGylated PAMAM. PAMAM macromolecules and PEG-PAMAM possessed strong containing capacity, besides, PEG-PAMAM showed better delayed drug release. Thus, PEG-PAMAM can be a good drug carrier for poorly soluble drug.

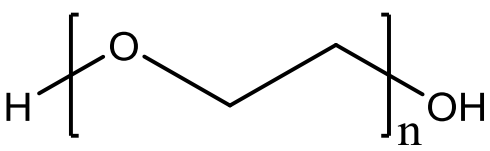


Figure 2 Structure of polyethylene glycol

3.2 Folic acid modification

Polyamide-amine macromolecule surface had a large number of end-group functional groups, which can be modified for different uses. It was found that folic acid was overexpressed in most tumor cells, and folic acid receptors were higher in the late tumor stage, so folic acid was thought to be a tumor marker. After modification of PAMAM with folic acid, the specific binding of folic acid to the folate receptor on the surface of the tumor cells can improve the active targeting of the gene vector PAMAM.

Liu Zhenlin et al[13] using folic acid modified PAMAM synthesized complex FA/PAMAM. They used tiny MRI-7 as the target gene, human glioma cell line U251 as the target cell line, observing the fluorescence transfection efficiency was higher compared with liposomes. MRI results showed that folic acid modified PAMAM group showed lower tumor volume growth rate and extended mouse survival.

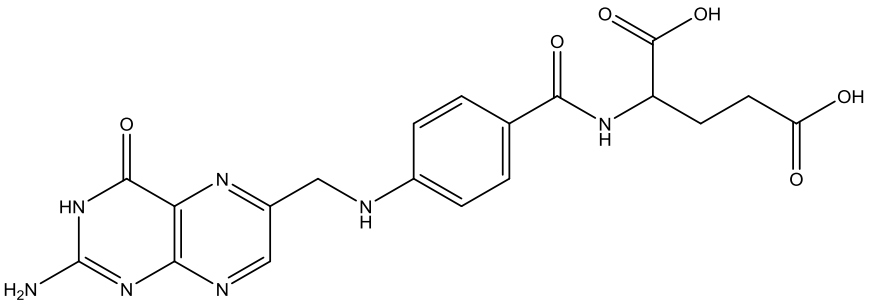


Figure 3 Structure of folic acid

3.3 Amino acid and peptides modification

Amino acids are essential nutrients to human body and which can be used as structural modifiers for PAMAM dendrimers. Basic peptides such as protein transduction domains (PTD) or membrane translocalization signals (MTS) are well investigated peptides in biomedical studies. Many studies had showed that the modified of hydrophobic amino acids and peptides on the surface of PAMAM changes the self-aggregation process between PAMAM and plasmid DNA, and ultimately improves the cell transfection efficiency[14, 15]. Y. Wen et al used Various amino acids such as lysine, arginine and histidine as well different peptides such as

Tat and RGD peptides to conjugate onto PAMAM structure[15]. Surface engineered PAMAM dendrimer by histidine possessed increased transfection efficiency. They observed that due to increased cellular uptake, as well as serum resistance, conjugation of histidine groups to PAMAM molecule could enhance DNA delivery. Thus amino acid or peptides modified PAMAM is a good way to improve the dendrimer stability, cell penetrating ability, transfection efficiency, and this kind of carrier could unload drug and targate into a specific cell or tissue.

## 4. PAMAM dendrimers in drug delivery applications

### 4.1 PAMAM dendrimers in oral delivery

Due to their ability to translocate across the gastrointestinal epithelium, PAMAM dendrimers have been extensively investigated in oral delivery. It is estimated the market of oral drug delivery is growing at a annual growth rate of 10.3 % from 2010 to 2017[16]. However, the challenges involved with oral drug delivery including the poor aqueous solubility, the acidic gastric environment, the stability of many drugs and the presence of digestive enzymes[17]. PAMAM dendrimers showed promise in enhancing oral delivery of drugs with poor bioavailability, and they can protect the drug in the acidic gastric environment. A more recent study involved investigation of PAMAM dendrimers as absorption enhancers for oral delivery of camptothecin, an anti-cancer agent with low oral bioavailability and gastrointestinal toxicity, and the results showed that PAMAM dendrimers can provide a platform for oral drug delivery[7]. In another study, oral absorption of PAMAM G3.0-$NH_2$-doxorubicin conjugate was investigated in rats. The results reported a 300 fold increase in bioavailability of the doxorubicin when delivered as PAMAM-doxorubicin conjugate as compared to the free drug following a single oral dose in rats[18].

### 4.2 PAMAM based targeted drug delivery in cancer therapy

PAMAM dendrimers are the most widely studied polymers used as vehicles for drug delivery, because of their multivalency, well-defined and globular structure, low

polydispersity. Untillnow, they are extensively investigated for various biomedical applications [19, 20] and selective tumor targeting [21-23]. Ugir Hossain Sk et al [11] developed a conjugate in which hydroxyl-terminated PAMAM dendrimer, G4-OH and PEG were used as carriers for the drug β-D-Arabinofuranosylcytosine (Cytarabine, Ara-C). The inhibition of cancer growth by the dendrimer-Ara-C and PEG-Ara-C conjugates was evaluated in A549 human adenocarcinoma epithelial cells. The results showed that both dendrimer-Ara-C and PEG-Ara-C conjugates were 4-fold more effective in inhibition of A549 cells compared to free Ara-C after 72 h of treatment. Also, Iulia Ioana Lungu et al reported that PAMAM-coated magnetic NPs are a promising targeted drug delivery system[24] that can encapsulate and release anticancer drugs such as DOX, with minimal side effects.

4.3 PAMAM dendrimer in gene delivery

PAMAM dendrimers could also used as vehicles in gene delivery system. Fant et al[25] reported that dendrimers can develop complexes with nucleic acid-like plasmid DNA (pDNA) through electrostatic interactions and bind to glycosaminoglycans (chondroitin sulphate, hyaluronic acid and heparan sulphate) on the surface of cell. Besides, Han and co-workers[26] employed peptide HAIYPRH (T7)-conjugated PEG-modified PAMAM dendrimer (PAMAM-PEG-T7) for the co-delivery of pDNA and doxorubicin. In comparison with single doxorubicin or pDNA delivery system, this co-delivery system induced apoptosis of tumor cells in vitro and inhibited tumor growth in vivo more efficiently. PAMAM dendrimers conjugated to proteins recognise receptors on the mesenchymal stem cell (MSC) membrane, shown by the generation 5.0 – 7.0 PAMAM dendrimers, which were able to deliver the hBMP-2 gene into MSCs and promote osteogenesis in vitro, even though their transfection efficiencies were low[27].

4.4 PAMAM dendrimer as improved contrast agents

PAMAM dendrimer are an attractive platform as improved contrast agents for

macromolecular imaging, because of the presence of multiple terminal groups on the exterior of the molecule. Metal ion chelates, large numbers of metal ions for imaging may be conjugated to the dendrimer in combination with a targeting vector to form contrast agents for macromolecular imaging[28]. With such potential, PAMAM-based MR imaging agents may replace other agents or when used in conjunction with other modalities provide greater levels of information. Current lymphangiography imaging techniques use fluorescence[29, 30], which has higher sensitivity than MRI, but only allows for superficial imaging. MRI, on the other hand, allows for accurate deep imaging through the use of large modified dendrimers, which increase blood retention and resolution[28].

## Conclusions and future outlooks

Dendrimers have received considerable attention in recent years due to their unique shape, small size and placement of functional groups that is desirable for many life science applications. PAMAM dendrimers were the first complete dendrimer family to be synthesized, characterized and commercialized. PAMAM dendrimers with high degree of uniformity, monodispersity and high density functional end groups are reported good drug carriers for application in drug delivery and biomedical. The toxicity of PAMAM dendrimers is a result of their intense surface positive charge under physiological conditions and nonselective interactions of PAMAM with both normal and tumor cells. However, after structure modification, PAMAM is a promising carrier in drug delivery system with considerable potential. This review provides a brief description about the structure and characteristics, the synthesis, the structure modification and the application of dendrimers. Overall, PAMAM is a promising could be a good drug delivery carrier with considerable potential.

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