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Review

An Overview on Surface Modified Dendrimers: Current Direction and Future Perspectives

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Abstract: Dendrimers are made up of synthetic and nano-sized molecules which represent a tree-like three-dimensional (3D) structure that delivers surface versatility and functionality. This review revealed that the surface modified agents like acetylation, polyphenols, and conjugation might be a promising nano-platform for more targeted site diagnosis, unique structural activity and higher bioavailability compatibility. Polyamidoamine (PAMAM) dendrimers are multipurpose nanocarriers, which can easily load with drugs and be amended by target-specific ligands, which are very specific to the receptor. PAMAM dendrimers are best suited for the release of hydrophobic drugs, as they can be encapsulated inside the internal void of PAMAM dendrimers. Moreover, current trends and future strategies, surface modification of dimensional globular nano-polymeric that are best for drug delivery are described with their potential applications in the biomedical sector. The aim of the present review article is to study the different methods of synthesis of dendrimers, how they can be modified with different methods as per the requirement, types of dendrimers and their use in different sectors.

***Keywords*:** dendrimers-based systems, drugs, synthesis, surface modifications or agents, functional agents, potential applications

1. Introduction

Dendrimers are synthetic macromolecules that have a tree-like appearance. They're known for their hyperbranched polymers, which can be surface tailored to a variety of chemical species and have a variety of therapeutic effects, including biomolecules, imaging agents, identification agents, medicinal agents, and bioanalytical applications. The term "Dendrimers" term came from two Greek words: "Dendron" (tree) and "Meros" (part). The arrangement of a dendrimer is made up of three fundamental components [1-3].

The structure of the dendrimer can be managed correctly, as dendrimer chains are grown sequentially by acquainting branch structures several times. Dendrimers are extraordinarily appealing nanomaterials for use in a variety of areas, including biomedical fields, due to their molecular consistency and ease in modification of their structure and properties [4, 5]. The transparent nanocomposite was developed from polyethylene glycol (PEG) and silicate nanoparticles with interconnected pores, high elongation and toughness. Besides its dental use, it was also beneficial as

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an elastic tissue matrix for orthopaedic and craniofacial applications. An elastomeric nanocomposite has been prepared from PEG and hydroxyapatite nanoparticles. Due to improvised mechanical properties, it was used in drug delivery as well as in the orthopaedic field. Carbon nano tube-gelatin methacrylate hybrids were synthesized and used in tissue engineering applications [6-8].

Synthesis of dendrimers takes place in either convergent or divergent methods to provide a spectacular shape (spherical) at nano size range with predictable characters. The divergent method involves the addition of monomers in repeated sequences and started from multivalent core to surface molecules with continuous enhancement in the number of branching. The molecular size and number of surface groups gradually increase with the addition of successive layers of monomers (generations) (Figure 1). While the convergent method involves the synthesis of dendrimers from the surface to the core and leads to the formation of wedge-shaped units or dendrons, these are joined to a multivalent core at the last step. This method has a lower risk of defect in the final structure rather than the divergent method, which often involves the appearance of incomplete branching. It is easy to modify the dendrimers by adding or modifying the functional groups. There are different techniques, which can be used to modify them like glycosylation, pegylation, conjugation, acetylation, polyphenols, etc. Many dendrimers are modified with these methods and details of these are given in Table 1-4 [9].

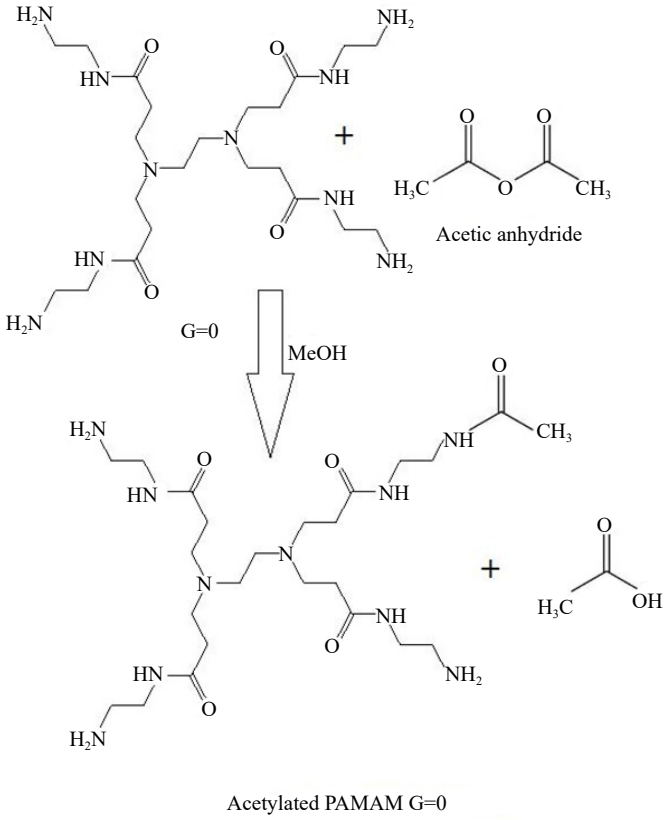

Figure 1. Scheme for the acetylation of polyamidoamine (PAMAM) dendrimer

Table 1. Dendrimers based on different surface modifications

Technique	Types of dendrimer	Linker	Application	Reference
Acetylation	PAMAM G5	Small interfering ribonucleic acid (siRNA)	To prevent the U87 malignant glioma cells	[10]
	PAMAM G5	Gold nanoparticles (Au NPs)	Neutralize the positive surface charge of the particles	[11]
	PAMAM G3	Fluorescein isothiocyanate (FITC)	Human colon adenocarcinoma cellular internalization. HT-29 cell line is a kind of cancer cell	[12]
	PAMAM dendrimers	1-Ethyl-3-(3-dimethylaminopropyl)	Through the absence of organic solvents, a significant amount of acetylation can be achieved in a shorter period of time	[13]
	PAMAM dendrimers	Au NPs	Engineering self-assembly of such nanoparticles	[14]
	PAMAM G5	Dendrimer-entrapped gold nanoparticles (Au DENPs)	Computed tomography (CT) imaging applications	[15]
	PAMAM G5	Moieties FITC and folic acid (FA)	Imaging agents and therapeutics	[16]
Conjugation	PAMAM G4	Doxorubicin (DOX) and monoclonal antibody-trastuzumab	Efficient in the drug delivery for tumors	[17]
	PAMAM G5	FA-DOX	Promising nanodevice for targeted cancer chemotherapy	[18]
	PAMAM G5	FITC + FA	Specific delivery of chemotherapeutic	[19]
	PAMAM G4	Drug-trastuzumab	A cancer cell enables targeted delivery	[20]
	PAMAM G4	PAMAM-DOX-glucose	Breast cancer cells	[21]
	PAMAM G3.5	FA conjugated to PEG-modified dendrimers / PAMAM with DOX and superparamagnetic iron oxide (Fe_3O_4) (FA-PEG-PAMAM-DOX@IONPs)	The relationship between magnetic resonance imaging (MRI) comparison and cancer treatment	[22]
	PAMAM G6	Peptide- and saccharide	Capturing and restraining colorectal circulating tumor cells (CTCs) in blood	[23]
	PAMAM G1-G4	Nucleic acids (deoxyribonucleic acid (DNA), siRNA, and micro-ribonucleic acid (miRNA))	Co-delivery systems are mainly for cancer therapy	[24]
	PEG- PAMAM G4	Mercaptohexadecanoic acid-functionalized gold nanorod (GNR)	Cancer therapy	[25]
	PAMAM G3	FITC	Normal fibroblasts and squamous carcinoma	[26]
	Pegylated PAMAM	Camptothecin	Nucleolin-overexpressed colorectal cancer	[27]
	PAMAM G5	Arginine and ornithine	Antigen/drug delivery	[28]
	PAMAM G4	Methotrexate (MTX)	Better cell killing efficiency than MTX	[29]
Glycosylation	PAMAM G1-G5	Glycan epitopes (Glu, Man, Gal and Lac)	Products show soluble and cellular lectin receptors	[30]
	PAMAM G3.5	64 peripheral carboxylic acid groups	Efficient in the treatment of inflammatory and malignant diseases	[31]
	PAMAM	MTX and d-glucose	Breast cancer	[32]
	PAMAM	Glycosylated siloxane-poly(amidoamine)	Highly sensitive fluorescent probes for a varied temperature range	[33]
	PAMAM G3.5	Glucosamine	Change in flexibility and polarity with varied glucosamine concentration	[34]
	Various generations of polypropylene imine (PPI) dendrimers	Star-shaped poly(glutamic acid)	These are architecture-dependent	[35]
	PAMAM	Glucosamine	Prevent gut wall tissue damage in diarrhoeal diseases	[36]

Polyphenols	mPEG-PAMAM (G3), mPEG-PAMAM (G4) and PAMAM (G4)	Release of drugs cisplatin, resveratrol, genistein and curcumin	Used as a device for the release of hydrophobic and hydrophilic drugs	[37]
	Carbosilane dendrimers	Vanillin	Cancer cell lines	[38]
	PAMAM G3 and G4	Resveratrol, genistein, and curcumin	In vitro release of polyphenols	[39]
	PAMAM	Electron donating groups (EDG) and antioxidant activities	Acting as an antioxidant against carbon and nitrogen free radicals	[40]
	PAMAM	Syringaldehyde- and vanillin +Cu(I)	Antioxidant activity	[41]
	PAMAM	Mitsunobu reaction and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) coupling agent	Enhanced quenching properties of free radicals	[42]
Pegylation	PAMAM	PEG	Effect pegylation of different biopharmaceutical properties of PAMAM dendrimers. Example: Solubility enhancement or drug loading	[43]
	PAMAM	PEG liposomal formulation Doxil	Effective as therapeutic and/or imaging applications	[44]
	PAMAM G4	Fully atomistic molecular dynamics (MD)	For drug delivery	[45]

Table 2. Dendrimer-based functional agents used in cancer therapy

Types of dendrimer	Functional agent	Application	Reference
PAMAM	GNRs	Photothermal therapy (PTT)	[45, 46]
	Indocyanine green (ICG)		
	Molybdenum disulfide (MoS_2)		
	Copper sulfate (CuS)		
	Au NPs		
PAMAM	Luciferase-targeted siRNA or Bcl-2 siRNA	Gene therapy	[47-50]
	Bcl-2 siRNA		
	siBcl-xl, siBcl-2 and siMcl-1 siRNAs		
PAMAM	DOX	Chemotherapy	[51]
PPI	DOX		[52]

Table 3. Dendrimers based on different surface modifications

Types of dendrimer	Surface modification agent	Function	Reference
PAMAM	PEG	Photothermal therapy (PTT)	[53, 54]
	Phosphorylcholine		
	Carboxybetaine acrylamide (CBAA)		
	Acetyl		
	CBAA		
	Arginylglycylaspartic acid (RGD)		
	Fluorochrome Cy5.5	Fluorescence imaging	[55]
PPI	Histidine, pyridine, piperazine	Buffering capacity property	[56]
	Anti-epidermal growth factor receptor variant III single chain fragment variables (anti-EGFRvIII scFv)	Targeting property	[57]
	Maltotriose	Reducing cytotoxicity	[58]
Phosphorous dendrimers	8-Anilino-1-naphthalenesulfonate	Fluorescence imaging	[59]

Table 4. Reactants and products for the preparation of PAMAM dendrimers, according to theory

No.	Generation of dendrimer	Theoretical molecular weight	Free NH_2 / COO^- groups
1	-0.5 G	406.01	4
2	0.0 G	51.09	4

1.1 *Acetylating of dendrimers*

Dendrimers are easily acetylated with acetic anhydride and lead to the formation of primary amine acetylation.

1.2 *Conjugation of dendrimers*

These can easily make drug conjugates by covalently bonding chemotherapeutic medicines to the dendrimer's outskirts. After the spacer between dendrimers and the drugs has been removed, the drugs should be released. As a result, the types of interfacing bonds are often associated with the drug discharge force. Amide linkage, hydrazone linkage, -(hydrazinosulfonyl) benzoic acid linkage, ortho-nitrobenzyl coupling, ester linkage, and disulfide linkage are the most common linkers (Figure 2) [6].

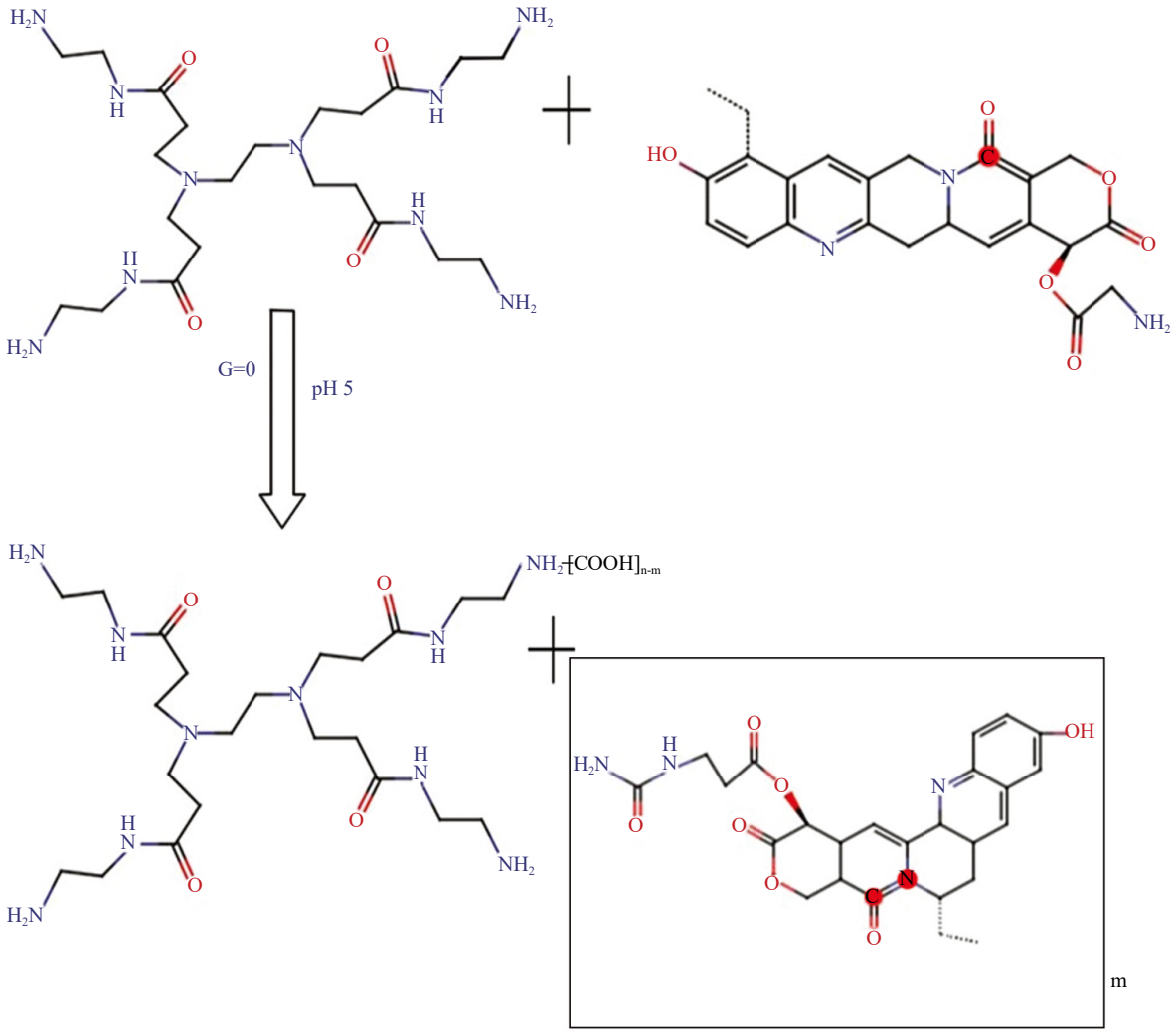

Figure 2. Scheme for conjugation of PAMAM dendrimers

1.3 *Glycosylation of dendrimers*

The beautification of these dendrimers is of their neutral charges, which improves their biocompatibility and thus can be used in the tissue engineering and biomedical sector. Glucose, maltotriose, mannose, lactose, etc. are mostly used sugar ligands in dendrimers. After that, halfway examination of these may be reduced to form optional and tertiary amines with the ideal starch units. These glycosylated dendrimers are evaluated as a device in drug delivery mechanism, as well as a medicinal, diagnosis, and therapy for leukemia [7-9].

1.4 *Polyphenols dendrimers*

Dendrimers are nanometer-sized synthetic macromolecules, which have heavily branched structures, that may be useful in drug delivery. Polyphenols have micronutrients and are available in the eating regimen, which plays a significant job in anticipation of degenerative sicknesses.

1.5 *Pegylation of dendrimers*

PEG substitution is the most widely used method for increasing dendrimer biocompatibility, extending dendrimer

blood flow time in vivo, and facilitating tumor collection via the enhanced penetrability and maintenance (EPR) effect. PEG acted as a spacer between dendrimers and concentrated on other utilitarian specialists (Figure 3) [9].

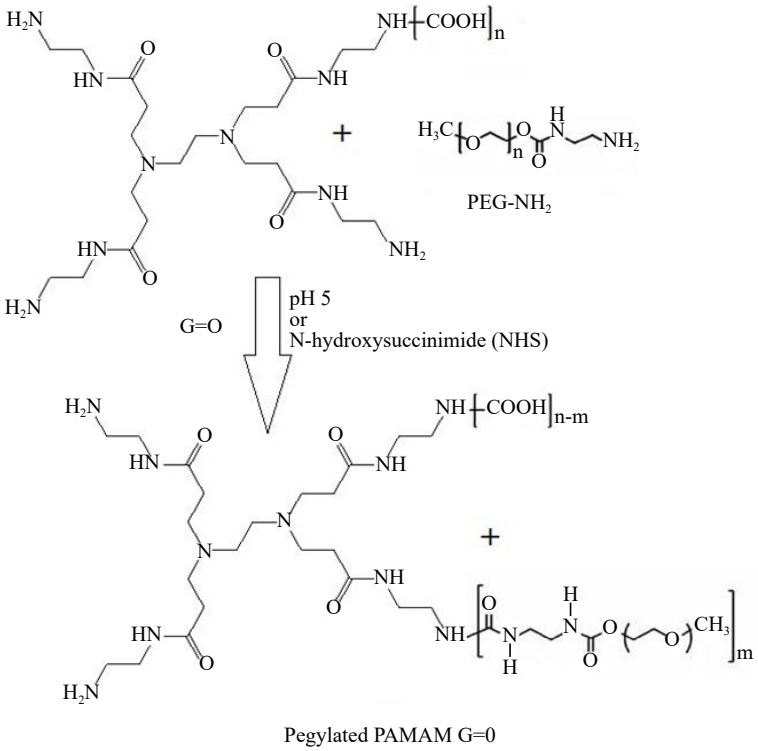

Figure 3. Scheme for pegylation of PAMAM dendrimers

1.6 *Synthesis of PAMAM Dendrimers*

PAMAM dendrimers are prepared using a contrary process. Preparation of an ethylenediamine (EDA) core PAMAM dendrimer involves two steps: In the first step, Michael addition of a primary amine to methyl acrylate and in the second step, amidation of the resulting multi ester of EDA (Figure 4) [60-62].

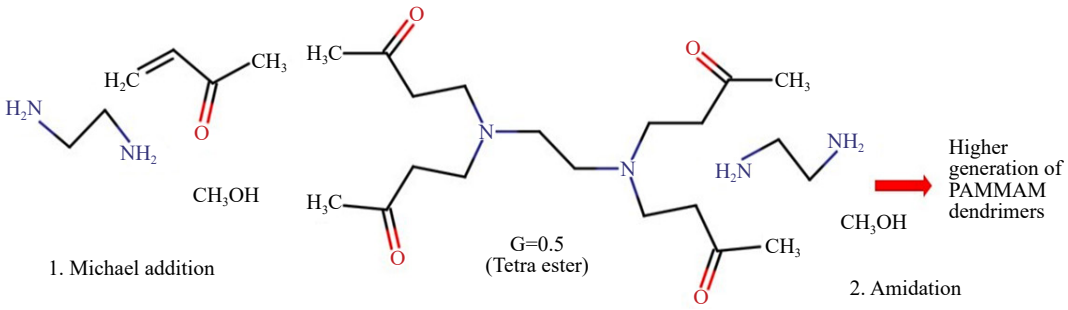

Figure 4. Scheme of synthesis of PAMAM dendrimer through Michael addition reaction

By adding 04 acrylate moieties in every group of EDA, it serves as an initiator centre for the beginning of the synthesis of dendrimers. The name given to the compound is generation -0.5 PAMAM tetra ester. The dendrimers'

arrangement branched as a result of this. The terminal carbomethoxy group ($COCH_3$) of methyl acrylate is amidated with EDA in step 2. “Generation 0.0 PAMAM tetra amine” was generated by combining this tetra ester with too much EDA. To prevent incomplete reactions and thereby boost yield, EDA can be used 30-100 times.

Methanol was used as a medium for the reaction. Any step of the reactions was followed by the removal of excess reagents by vacuum evaporation at 50-60 °C. The entire reaction took place in the dark and in an amber-colored firmly corked circular flask. The reaction was completed in two days, while the amidation reaction took four days [9, 60-62].

2. Synthetic methodology

2.1 *Synthesis of PAMAM dendrimers of the -0.5 generation*

In a beaker, combine EDA (3.5 ml) with a minimal amount of methanol. Methyl acrylate (19.5 ml) and a small amount of methanol were combined separately. Both solutions were combined in an amber-colored rubidium fluoride (RbF) and set aside for 48 hours. A CuS test was used to track the reaction. The solvent was extracted under a vacuum at 52 °C after the reaction was completed. PAMAM dendrimers of the -0.5 century were shaped as a semisolid mass.

2.2 *Synthesis in PAMAM dendrimers of the first generation*

An amount of 2 g of -0.5 G + EDA (41.6 ml) was dissolved in 12-18 ml methanol in an amber-colored circular bottom flask that was securely corked and stored for 72 hours. Finally, any remaining liquid is ejected into the water bath. Ultraviolet (UV) spectroscopy and Fourier transform infrared (FTIR) spectroscopy are used to examine the dendrimers that have been prepared.

2.3 *Surface modification of PAMAM dendrimers*

Refer to Figures 1, 2 and 3.

3. Conclusion

Dendrimers are profoundly characterized by artificial macromolecules. They are described by a mix of a high number of combinations of molecular structure and functional groups. Dendrimers could be functionalized with different groups of surfaces modified which show more therapeutic efficacy and targeting agents. PAMAM dendrimers are best suited for the release of hydrophobic drugs, as they can be encapsulated inside the internal void of PAMAM dendrimers. Their pH-sensitive and low pH properties provide a stimulus for the release of the drug. The surface decoration acetylation, pegylation, glycosylation, polyphenols, and conjugation unique structural show significant properties of dendrimers for cancer therapy, synergistic therapeutic efficacy, multifunctional nano drug delivery, higher biocompatibility, and enhanced treatments.

Conflict of interest

Declared none by all authors.

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