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Dendrimers: A New Class of Nanoscale Polymer for Healthcare System

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ABSTARCT

Dendrimer chemistry is one of the most fascinating and rapidly expanding areas of modern chemistry. Dendrimers are a unique class of synthetic macromolecules having highly branched, three dimensional, nanoscale architecture with very low poly dispersity and high functionality. Dendritic polymers are belonging to hyper-branched macromolecules. Similar to linear polymers, they composed of a large number of monomer units that were chemically linked together. Due to their unique physical and chemical properties, Dendrimers have wide ranges of potential applications. The advantages of dendritic structures for property modification and their potential applications in very diverse areas are illustrated. The exciting merger of dendrimer chemistry with self-assembly offers new, stimulating avenues for exploration. These include drug-delivery systems, medical diagnostics, gene therapy, treatment of diseases, adhesives and coating, chemical sensors, catalysts, building blocks of super molecules, separation agents and many more. Cationic surfaces show cytotoxicity however, derivatization with fatty acid or PEG chains, reducing the overall charge density and minimizing contact between cell surfaces and dendrimers, can reduce toxic effects. This review briefly discusses the various aspect of dendrimer including properties, preparation of dendrimers types, characterization, dendrimer based products and their use as pharmaceutical, therapeutic, diagnostic agent and their potential for applications in drug delivery.

KEYWORDS: Dendrimers, Biocompatibility, Drug delivery, Polyamidoamine (PAMAM)

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1. INTRODUCTION:

Dendrimer, is derived from the greek word (dendron) for tree, refers to a synthetic, three dimensional molecule with branching parts[1]. Dendrimers were invented in the late 1970's by Donald tomalia, a chemist working for the dow chemical corporation, Michigan. At the same time prof. Gorge R. Newkome's group (university of akron, USA) independently reported synthesis of similar macro molecules[2]. They called them arborols from the latin word arbor also meaning a tree. The term cascade molecule is also used, but dendrimer is the best established one. Dendrimers are a new class of man made molecules produced by an unusual synthetic route which incorporates repetitive branching sequences to create a unique novel architecture[3]. Exceptional features of the dendritic architecture include a high degree of structural symmetry, a density gradiant displaying an intramolecular minimum value and a well defined number of terminal groups which may be chemically different from the interior. The combination of these features creates an environment within the dendrimer molecule facilitates an avenue to developing reliable and economical fabrication and manufacturing of functional nanoscale materials that would have unique properties (magnetic, chemical, or biological) that could be the basis of new nanoscale technology and devices[4-5].

2. SYNTHESIS:

Dendrimers are generally prepared using either a divergent method or a convergent one. There is a fundamental difference between these two constructive concepts in the **divergent methods [A]**, dendrimer grows outwards from a multifunctional core molecule.The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation Dendrimers then the new periphery of the molecule is activated for reactions with more monomers. the process is repeated for several generations and a dendrimer is built layer after layer. The divergent approach is successful for the production of large quantities of Dendrimers problems occur from side reactions and incomplete reactions of the and group that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagent is required. It causes some difficulties in the purification of the final product.

The convergent methods [B], were developed as a response to the weaknesses of the divergent synthesis. In the convergent approach, the Dendrimers is constructed stepwise, starting from the end groups and progressing inwards[6]. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule. The convergent growth method has several advantages[7]. It is relatively easy to purify the desired product and the occurrence of defects in the final structure is minimized. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecules. The convergent approach does not allow the formation of high generations because steric problem occur in the reactions of the dendrons and the core molecules. The first synthesized Dendrimers were polyamidoamines (PAMAMs)[8]. Ammonia is used as the core molecule. In the presence of methanol it reacts with methyl acrylate and then ethylene diamine is added.

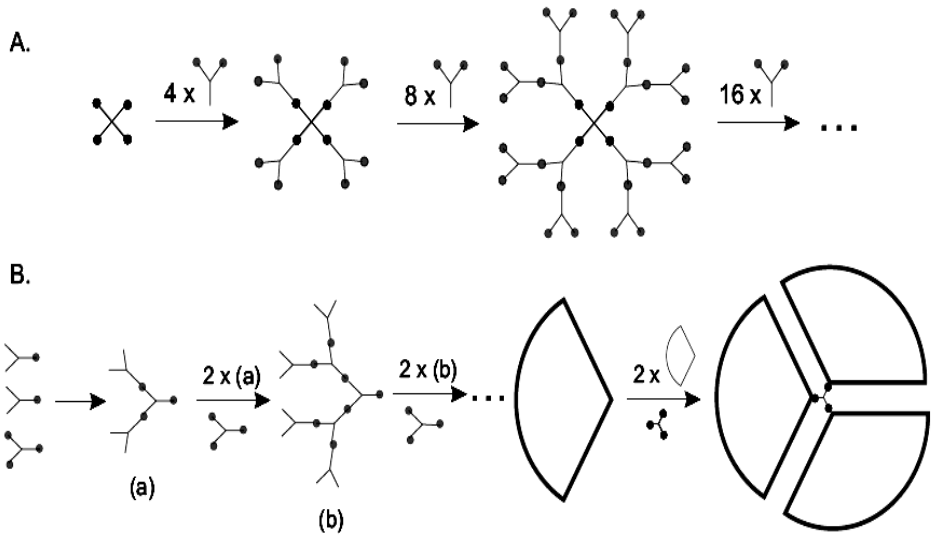

Figure 1: A. The divergent growth method; B. The Convergent growth method

$$NH_3 + 3CH_2CHCOOCH_3 \longrightarrow N(CH_2CH_2COOCH_3)$$

$$N(CH_2CH_2COOCH_3)_3 + 3NH_2CH_2CH_2NHN \longrightarrow (CH_2CH_2CONHCH_2CH_2NH_2)_3 + 3CH_3O$$

At the end of each branch there is a free amino group that can react with two methyl acrylate monomers and two ethylene diamine molecules. Each complete reaction sequence results in a new dendrimer generation. The half generations PAMAM dendrimers (e.g. 0.5, 1.5, and 2.5) possess anionic surfaces of carboxylic groups.

The number of reactive surface sites is doubled with every generation. The mass increases more than twice. The molar mass of the dendrimer can be predicted mathematically:

$$M = Mc + nc.\left[Mm.\left(\frac{nGm-1}{nm-1}\right) + Mt.nGm\right]$$

Where: M_c – is the molar mass of the core, M_m – the molar mass of the branched monomer, M_t – the molar mass of the terminal groups, n_c - the core multiplicity, nm – the branched-juncture multiplicity, G – the generation number[9].

2.1 MOLECULAR STRUCTURE:

Dendrimers of the lower generations (0, 1 and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become higher and more branched (in 4 and higher generations) dendrimers adopt a globular structure[10]. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space[11]. This is called the 'starburst' For PAMAM dendrimers synthesis it is observed after tenth generation. The rate of reaction drops suddenly and further reaction of the end groups cannot occur[12].

2.2 PROPERTIES:

Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis[13]. Because of their molecular architecture, dendrimer show some significantly improved physical and chemical properties when compared to traditional linear polymer. In solution, linear polymers solution linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball[14]. This has a great impact on their rheological properties. Dendrimer solutions have significantly lower viscosity than linear polymers. When the molecular mass of dendrimer increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline. Such behavior is unlike that of linear polymers. For classical polymers the intrinsic viscosity increases continuously with molecular mass. The presence of many chain ends is responsible for high solubility and miscibility and for high reactivity.dendrimers' solubility is strongly influenced the nature of surface groups[15-16]. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. Dendrimers have some unique

properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in macromolecule interior[17]. Meijer and coworkers trapped small molecules like rose Bengal or p-nitro benzoic acid inside the 'dendritic box' (Fig. 2) of poly (propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting the terminal amines with an amino acid (L-phenylalanine) and guest molecules were stably encapsulated inside the box. Hydrolyzing the outer shell could liberate the guest molecules. Meijer's group described experiments in they had trapped four molecule of the rose bangal or eight to ten molecules of p-nitrobenzoic acid in one dendrimer[18]. Archut and co-workers developed a method in which boxes could be opened photochemically.

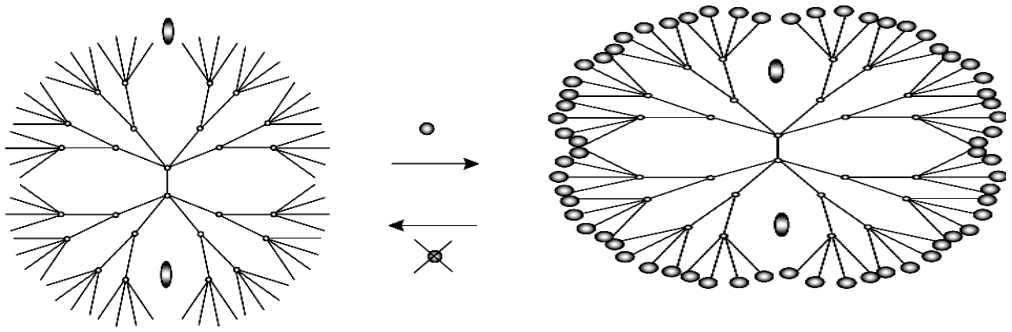

Figure 2: Dendritic box, encapsulating guest drug molecules.

A fourth generation polypropylene iminine dendrimer with 32 end groups was terminated in azobenzene groups (Fig. 3). The azobenzene groups undergo a fully reversible photoisomerization reaction The E isomer is switched to the Z form by 313 mm light and can be converted back to the E form by irradiation with 254 nm light or by heating. Photochemical modification of the dendritic surface causes encapsulation and release of guest molecules. Archut's experiment demonstrated that the Z form of the forth generation dendrimers are better host than the E forms[19].

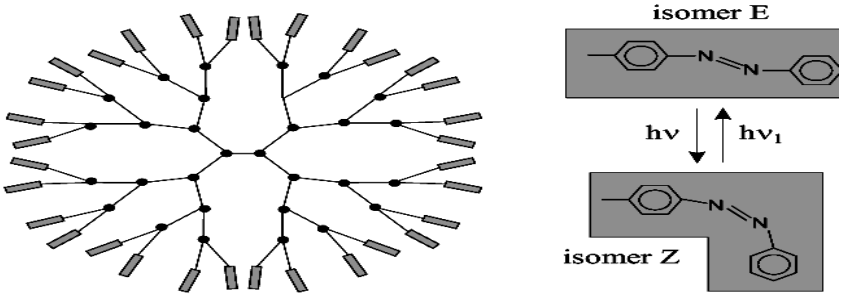

Figure 3: Dendrimers Terminated in azobenzene groups.

Biological properties of the dendrimers are crucial because of the growing interest in using them in biomedical application. "Cationic" dendrimers (e.g., amine terminated PAMAM and poly (propylene imine) dendrimers that form cationic group at low pH) are generally haemolytic and cytotoxic. Their toxicity is generation dependent and increases with the number of surface group. PAMAM dendrimers (generation 2, 3 and 4) interact with erythrocyte membrane proteins causing change in protein conformation. These changes increase with generation member and the concentration of dendrimers. The interactions between proteins and half generation PAMAM dendrimers (2.5 and 3.5) are weaker[20]. Anionic dendrimers, bearing a carboxylate surface, are not cytotoxic over a broad concentration range. Incubation of human red blood cells in plasma or suspended in phosphate-buffered saline with PAMAM dendrimers causes the formation of cell aggregates. No changes in aggregability of nucleated cells such as Chinese hamster fibroblasts are observed.

2.3. APPLICATIONS:

Dendrimers are "stealth molecules" that have many potential applications. By customizing and controlling dendrimers "architecture", nanotechnologies are developed dendrimers for drug delivery, diagnostics, therapy, biomedical, and other significant industrial applications. Dendrimers can easily move across biological membranes and they can store a wide range of the metals, organic and inorganic molecules among their branches. Companies developing these synthetic molecules claim that most dendrimers do not trigger the immune system when injected or used topically, have the low cytotoxicity (that is, toxicity to cells). However some forms of dendrimers can induce the clotting in the bloodstream- a potential concern for in vivo applications[21]. Dendrimers have been applied in delivery of drugs, they can be used as drug carriers, drugs can be encapsulated with in dendrimers to deliver into the biological system, apart they can also used as dendrimer-drug conjugates, biodegradable dendrimer polymers has also been developed. Controlled release dendrimers has the benefit of controlled release of the drug from the dendrimer-drug conjugates systems. Dendrimers can also be used as coating agents to protect or deliver the drugs to specific sites in the body or as time release vehicles for biological active agents. 5-fluorouracil (5FU) is known to have remarkable antitumor activity, but it has high toxic side effects. PAMAM dendrimers after acetylation can form the dendrimer-5FU conjugates[22]. The dendrimers are water soluble and hydrolysis of the conjugates releases free 5FU. The slow release reduces 5FU toxicity. Such dendrimers seem to be potentially useful carriers for antitumor drugs. In *in vitro* diagnostics, dendrimers are being used for cardiac testing. Proteins present in a blood sample bind to the immunoglobulins which are fixed by dendrimers to a sheet of glass. The result shows if there is any heart muscle damage. This method significantly reduces the waiting time for blood test results (to about 8 minutes). When a randomly organized solution of immunoglobulins is used the test lasts up to 40 minutes[23]. Conjugates

of dendrimer and antibody improve also the precision and sensitivity of the test. Dendrimer based metal chelates are being used as a new class of magnetic resonance imaging contrast agents for diagnostical imaging of the organs and blood vessels. Avidin-dendrimer is a tumor targeting therapeutic agent for intraperitoneal disseminated tumor which can be dully water-soluble lipopolymer (WSLP), which consist of polyethyleneiminine (PEI, 1800 Da) and cholesterol is characterized as a gene carrier to smooth muscle cells and myocardium. Dendrimers are also used for gene transfer. Although these cationic molecules show promise as versatile DNA carriers, very little is known about the mechanism of gene delivery but probably suggested that it operates via a cholesterol dependent pathway[24]. In the treatment of cancer, dendrimers are already used to target tumors, and to that their drug carrier ability is used in such treatment, dendrimers carry boron clusters into the cancer cells. Boron is a heavy absorber of neutrons, so when the tumor is irradiated with a neutron beam, the boron nuclei absorb energy, releasing it as short-range, but deadly, X-rays, killing the cells they are in. but the neutrons pass relatively harmlessly through the healthy cells, producing little damage[25]. Dendrimer based products include, for example A dendrimer based tool for detecting cardiac damage is being developed by Dade Behring, one of the world largest medical diagnostic firms. The world's first drug based on dendrimers, developed by Australian –based Star pharma, is a topical gel for use as a "liquid condom" to reduce the risk of HIV infection in women. Star pharma's "Vivagel" microbicide has gone through initial animal testing and phase-one safety trials in humans. The US army research laboratory is developing a dendrimer-based anthrax detecting agent, dubbed "Alert Ticket"[26-27].

3. CONCLUSION & PROSPECTS:

The designing aspects of dendrimers can be control carefully. One can synthesize dendrimer with certain molecular mass and structural confirmation. The unique physical and chemical properties of dendrimers have demonstrated great versatilities in variety of applications. A rapid increase of interest in the chemistry of dendrimers has been observed since the first dendrimers were synthesized. At the beginning work concentrated on the method of synthesis and investigation of properties of the new class of macromolecules. Soon first application appeared. Despite two decades since the discovery of dendrimers the multi- step synthesis still requires great efforts. Unless there is a significant break through in this field, only few applications for which the unique dendrimer structure is crucial will pass the cost-benefit test.

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