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Review Article

DENDRIMER: THE RECENT DRUG DELIVERY SYSTEM

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ABSTRACT
Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules (meaning of a consistent size & form). The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behavior dendrimers are suitable for a wide range of biomedical and industrial applications. They possess empty internal cavities & many functional end groups which are responsible for high solubility & reactivity. They are produced in an interactive sequence of reaction steps, in which each additional interaction leads to a higher generation dendrimer.
Key Words: Dendrimer, higher generation dendrimer

INTRODUCTION

First discovered in the yearly 1980's by Donald Tomalia and co-workers[1], these hyper branched molecules were called dendrimers. The term originates from 'dendron' meaning a tree in Greek. At the same time, Newkome's group[2] independently reported synthesis of similar macromolecules. 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 possess three distinguished architectural components namely

(I) Iinitiator core

(II) Interior layers (generations) composed of repeating units, radically attached to the interior core.

(III) Exterior (terminal functionality) attached to the outermost interior generations.

Synthesis

Dendrimers are generally prepared using either a divergent method or a convergent[3] there is a fundamental difference between these two construction concepts. In the divergent methods, 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 dendrimer. 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 end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required.

The convergent methods were developed as a response to the weaknesses of the divergent synthesis[4]. In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards. 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. 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 macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule. The first synthesized dendrimers were polyamidoamines (PAMAMs). They are also known as starburst dendrimers[5]. The term 'starburst' is a trademark of the Dow Chemicals Company. Ammonia is used as the core molecule. In the presence of methanol it reacts with methyl Acryl ate and then ethylenediamine is added.

At the end of each branch there is a free amino group that can react with two methyl acryl ate monomers and two ethylenediamine molecules. Each complete reaction sequence results in a new dendrimer generation. The half-generation PAMAM dendrimers (e.g., 0.5, 1.5, 2.5) possess anionic surfaces of carboxyl ate groups. The number of reactive surface sites is doubled with every generation. The mass increases more than twice.

Types of Dendrimers

1. PAMAM Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents, a molecular weight of over 9, 30,000 g/mol have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, usually as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

2. PAMAMOS Dendrimer

Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors.

3. PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle.These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines.

4. Multilingual Dendrimers

In these dendrimers, the surface contains multiple copies of a particular functional group.

5. Chiral Dendrimers

The chirality in these dendrimers is based upon the construction of a constitutionally different but chemically similar branches to chiral core.

6. Hybrid Dendrimers Linear Polymers

These are hybrids (block or graft polymers) of dendritic and linear polymers.

7. Amphiphilic Dendrimers

They are built with two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

Advantages of Dendrimers in Comparison with other 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. Dendrimers are monodisperse macromolecules, unlike linear polymers. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological (it's property of the flow behavior) properties.

Applications

Dendrimers have been tested in preclinical studies as contrast agents for magnetic resonance. Magnetic resonance imaging (MRI) is a diagnostic method producing anatomical images of organs and blood vessels. Placing a patient in a generated, defined, inhomogeneous magnetic field results in the nuclear resonance signal of water, which is assigned to its place of origin and converted into pictures? Addition of contrast agents improves sensitivity and specificity of the method. Gadolinium salt of diethylenetriaminepentaacetic acid (DTPA) issued clinically but it diffuses into the extra venous area due to its low molecular mass[6]. Dendrimers due to their properties are highly suited for use as image contrast media. Several groups have prepared dendrimers containing gadolinium ions cheated on the surface[7, 8].

There are attempts to use dendrimers in the targeted delivery of drugs and other therapeutic agents. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups.Sialylated dendrimers, called sialodendrimers. Dendrimers can be used as coating agent's to protect or deliver drugs to specific sites in the body or as time-release vehicles for biologically active agents. 5-Fluorouracil (5FU) is known to have remarkable antitumour activity, but it has high toxic side effects. PAMAM dendrimers after acetylating can form dendrimer-5FU conjugates[9]. 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 antitumour drugs.

Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Currently liposomes and genetically engineered viruses have been mainly used for this. PAMAM dendrimers have also been tested as genetic material carriers[10, 11].

Recent advancement of Dendrimer in cancer therapy

With an eye toward developing a delivery vehicle for anticancer agents that are poorly soluble in water, a research team at Boston University and the Research Triangle Institute (RTI) has developed a biocompatible dendrimer that wraps itself around water-insoluble drugs. The investigators have used this dendrimer to create water-soluble formulations of three promising anticancer agents belonging to the camptothecin family, which also includes the widely used drugs topotecan. This research is reported in the journal Cancere search. Polyamidoamine (PAMAM) dendrimers has received much attention for their ability to solubilize water-insoluble drugs and their ability to promote the transport of drugs across biomembranes. In one study an efficient transdermal drug delivery system (TDDS) consisting of a polyhydroxyalkanoate (PHA)-based system with a polyamidoamine dendrimer was examined for the transdermal delivery of tamsulosin. By adding the dendrimer, the dendrimer-containing PHA matrix achieved the clinically rerequired amount of tamsulosin permeating through the skin model

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Table 1: Properties of Dendrimer and linear polymers

Sr. No.	Property	Dendrimers	Linear Polymers
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	Crystallanity	Non-crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7	Aqueous solubility	High	Low
8	Nonpolar solubility	High	Low
9	Viscosity	Non linear relationship with molecular weight	Linear relation with molecular weight
10	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydisperse