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Review Article

DENDRITIC ARCHITECTURE: A NEW TOOL FOR DEVELOPMENT OF NOVEL DRUG DELIVERY SYSTEMS

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ABSTRACT
Dendrimers are composed of a multifunctional core molecule attached to polymer branches. Drugs can be inserted between the branches and held until 'interactions' release it. Dendrimers are a new class of three-dimensional, man-made molecules produced by an unusual synthetic route which incorporates repetitive branching sequences to create a unique novel architecture. Exceptional features of the dendritic architecture include a high degree of structural symmetry, a density gradient displaying an intra-molecular 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 (electronic, optical, opto-electronic, magnetic, chemical, or biological) that could be the basis of new nanoscale technology and devices.
KEYWORDS: Dendritic Architecture, Properties, Nomenclature, solubility, Applications, New tools

INTRODUCTION

Dendrimers are spheroid or globular nanostructures that are precisely engineered to carry molecules encapsulated in their interior void spaces or attached to the surface. Size, shape, and reactivity are determined by generation (shells) and chemical composition of the core, interior branching, and surface functionalities. Dendrimers are constructed through a set of repeating chemical synthesis procedures that build up from the molecular level to the nanoscale region under conditions that are easily performed in a standard organic chemistry laboratory. The dendrimer diameter increases linearly whereas the number of surface groups increases geometrically. Dendrimers are very uniform with extremely low polydispersities, and are commonly created with dimensions incrementally grown in approximately nanometer steps from 1 to over 10nm. The control over size, shape, and surface functionality makes Dendrimers one of the "smartest" or customizable nanotechnologies commercially available [1, 2, 3, 5].

Newkome's group 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 used[3].

Dendrimer represents a novel type of polymeric material. It is also known as starburst or cascade or molecular trees or arborols, or polymers. They attract the increasing attention of all because of their unique structure, high degree of control over molecular weight and the shape that has led to the synthesis of unimolecular micelles[4].

The problem is that these molecules possess an enormous number of energetically permissible conformations, and in solution there is rapid interchange between them. Thus diffraction techniques yield little structure information. Also a number of generations involve the same monomers, making it difficult to extract precise information about the local structure from infrared or NMR experiments. Thus the most precise experimental data about overall structure comes from size exclusion chromatography (SEC) [6, 7, 8]. The main experimental data about the geometric character of particular sites has come from NMR relaxation times for molecules able to partially penetrate into the dendrimer [9]. The rapidly accelerating research and development activities in dendrimers and dendritic materials provide critically needed nanoscale building blocks suitable for the development of high performance materials[10].

PROPERTIES OF DENDRIMERS[8, 9, 11, 13, 34]

Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse, macromolecules. 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. The paper gives a concise review of dendrimers' physico-chemical properties and their possible use in various areas of research, technology and treatment.

These properties include:

Efficient Membrane Transport - Dendrimers have demonstrated rapid transport capabilities across biological membranes.

High Loading Capacity - Dendrimers structures can be used to carry and store a wide range of metals, organic or inorganic molecules by encapsulation and absorption.

High Uniformity And Purity - The synthetic process used produces dendrimers with uniform sizes, precisely defined surface functionality, and very low impurity levels.

Low Toxicity - most dendrimer systems display very low cytotoxicity levels

Low Immunogenicity- Dendrimers commonly manifest a very low or negligible immunogenic response when injected or used topically.

Physicochemical Properties

Unlike classical polymers, dendrimer have a high degree of molecular uniformity, narrow molecular weight distribution,

specific size and shape characteristics, and a highly functional terminal surface. The branching nature of the structure can lead to large 3-D globular structures, which at high molecular weights may approximate spheres. These structures are relatively fixed, in marked contrast to linear polymers that are random coils and, contrast to linear polymers that are random coils and, configurations. Many of the physical properties of Dendrimers may be predicted, at least qualitatively, from molecular modeling of the growth process. With the PAMAM Dendrimers, a fully developed dendrimer structure first appears only after dendrimer growth to at least G1.5, since it is not until the point that the dendrimer contains all three branch cell components, i.e., the core, interior and surface branch cells. This transition from lightly branched structures to fully developed dendriditic structure is referred to as the critical branching stage[14, 15, 18.]

Because of the progressive growth pattern, the Dendrimers are constructed in a precise manner and a linear increase of the radii of the fully developed dendrimers with increase of generation is expected. However, because the surface cells amplify according to a geometric progression with increasing generation, it is clear that ideal growth cannot continue indefinitely and there will be a critical generation at which the reacting dendrimer surface will not have sufficient space to accommodate all of the required new units. This stage is referred to as the de Gennes dense-packed state and occurs around G7 in the PAMAM Dendrimers. Dendritic growth beyond this point is of course possible but leads to products of imperfect structure because not all of the surface groups are able to participate in reaction due to steric effects. Such defective generations have been called "hairy dendrimers"[16, 19].

Surface Properties Of Dendrimers

The surface properties of Dendrimers are specific to the functional terminal groups that make up the surface of the Dendrimers, which can be either reactive or passive moieties or even a combination of both. The type and number of functional groups and their ionization characteristics may affect dendrimer solution properties in various ways, e.g., by changing the solubility, potential for aggregation, and inter-dendrimer charge interaction. A dendrimer surface may contain multiple copies of a particular functional group and so would be an ideal molecule for substrate binding. Under conditions where the functional groups are ionized, the dendrimer becomes a macromolecular polyelectrolyte and as such it will interact strongly with oppositely charged particles. Polyelectrolyte Dendrimers have been shown to adsorb strongly at various interfaces such as alumina/water and silica/water as well as associating with proteins or DNA[20, 21, 22, 29].

Flow Properties And Inter-Dendrimer Interaction

The flow properties of solutions of Dendrimers have relevance not only for their possible use in pharmaceutical formulation, but also because of the insight that might be gained on the nature of any intermolecular interactions between Dendrimers. It might be expected from computer modeling of the dendrimer shape that lower generations, which have an open "plate-like" or "dome-like" entity, would readily permit a branch from a neighboring dendrimer to penetrate into the interior. This tendency would be further enhanced by intermolecular hydrogen bonds between the interior amide groups of two interpenetrating molecules or between the primary amine units of one molecule and the amide carbonyl oxygens of another. In contrast, the closure of the dendrimer outer surface at higher generations should result in minimal inter-dendrimer interactions[17, 18].

Internal Structure

Many of the potential applications of Dendrimers depend directly on the organization and distribution of internal segment densities and the possibility of reduced density the core. The first theoretical treatment of internal structure of the amine-terminated PAMAM Dendrimers by de Gennes and Hervet predicted a segment distribution function that has the highest density on the periphery and a relatively hollow core[23].

Unique Properties Of Dendrimers

The unique properties of dendrimers, such as their high degree of branching, multivalency, globular architecture and well-defined molecular weight, make them promising new scaffolds for drug delivery. In the past decade, research has increased on the design and synthesis of biocompatible dendrimers and their application to many areas of bioscience including drug delivery, immunology and the development of vaccines, antimicrobials and antivirals. Recent progress has been made in the application of biocompatible dendrimers to cancer treatment, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin, as well as agents for both boron neutron capture therapy and photodynamic therapy. Dendrimers are highly branched and multivalent macromolecules that are emerging as promising new backbones for the development of drugs and nanoparticulate drug delivery vehicles[24].

Drug Delivery By Dendrimers

An ideal drug delivery system possesses two elements: the ability to target and controlled release. Targeting will ensure a high efficiency of the drug and possibly reduces side effects of the drug. The reduction or even prevention of side effects can also be achieved by controlled release. Modified dendrimers can be used to carry drug molecules to a specific location and release them in a controlled way[25, 26].

SYNTHESIS OF DENDRIMERS

Dendrimers are generally prepared using either a divergent method or a convergent one. There is a fundamental difference between these two construction concepts[3].

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 (Figure 2). 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. It causes some difficulties in the purification of the final product[27].

The **Convergent Methods** were developed as a response to the weaknesses of the divergent synthesis. 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

(Figure 3). 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 [27, 28].

Scheme no: 1 Ammonia Reacts With Methylacrylate

The first synthesized dendrimers were polyamidoamines (PAMAMs). They are also known as starburst dendrimers. 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 methylacrylate and then ethylenediamine is added[12].

Scheme no: 2 Ammonia Reacts With Ethylenediamine

At the end of each branch there is a free amino group that can react with two methyl acrylate monomers and two ethylenediamine molecules. Each complete reaction sequence results in a dendrimer generation. The half generations PAMAM dendrimers (e.g., 0.5, 1.5, and 2.5) possess anionic surfaces of carboxylate groups. The number of reactive surface sites is doubled with every generation (Figure 1). The mass increases more than twice [(14).]

Synthesis Of PEGylated Dendrimers

Dendrimers are precisely defined, synthetic nonmaterial's that are approximately 5-10 nanometers in diameter. They are made up of layers of polymer surrounding a central core. The dendrimer surface contains many different sites to which drugs may be attached and also attachment sites for materials such as polyethylene glycol (PEG) which can be used to modify the way the dendrimer interacts with the body.

PEG can be attached to the dendrimer to 'disguise' it and prevent the body's defense mechanisms from detecting it, thereby slowing the process of breakdown. This allows the delivery system to circulate in the body for an extended time period, maximizing the opportunities for the drug to reach the relevant sites [30].

DENDRIMER RHEOLOGY

Examining the rheological (flow) behavior of dendrimers in solution is a very powerful tool for exploring the relationship between molecular structure and macroscopic behavior. The exciting recent result of it is possible to produce complex materials with behavior and properties exhibiting both polymeric and colloidal features[31].

By altering the spacer lengths in well-defined dendritically branched polystyrene solutions, they show that the scaling of viscosity with concentration can be made to span the entire range of behavior between the limits. To date, there appear to be no theoretical descriptions of this dependence of the viscosity on concentration. Indeed, the description of concentration effects in linear polymer-solvent systems within the framework of exact Brownian dynamics simulations has only recently been attempted [32].

The main stumbling block so far has been the significant increase in CPU time in comparison to dilute solutions due to the presence of inter-molecular interactions. Recently, however, novel simulation algorithms for concentrated colloidal suspensions have been developed that lead to a significant reduction in CPU time. These advances will be incorporated into the dendrimer solution simulation algorithms that will be developed under this research program, enabling the exploration of the dependence of rheological properties on concentration. Basically, once the fundamental difference in the molecular architecture is taken into account, the microscopic physics that governs the behavior of dendrimers is identical to that which governs the behavior of linear polymers [33].

CONCLUSION

The literature review of dendritic architecture was suggested that dendrimer have a high degree of molecular uniformity, narrow molecular weight distribution, specific size and shape characteristics and a highly functional terminal surface. It has rapid transport capabilities across biological membranes. It can be easily synthesized in the laboratory. High molecular weight compound can be easily transported via dendrimer without producing toxic effect. This is the new tool for researcher for development of novel drug delivery system. At present so many research are ongoing with different biopharmaceutical classes using dendritic architecture.

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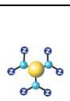
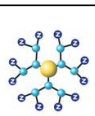
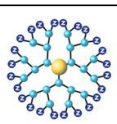
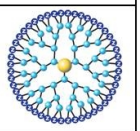
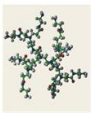
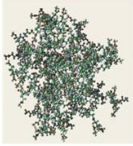
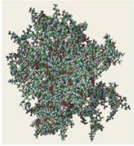
Generation	G0	G1	G2	G3	G4
# of Surface Groups	3	6	12	24	48
Diameter (nm)	1.4	1.9	2.6	3.6	4.4
2D Graphical Representation					
3D Chemical Structure View					

Figure 1: Dendrimer Nomenclature [2]

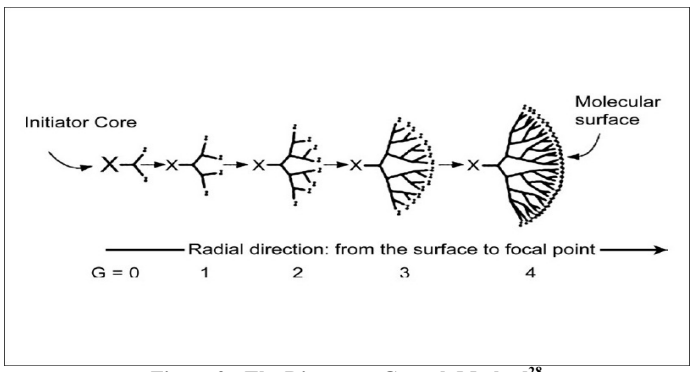


Figure 2: The Divergent Growth Method[28]

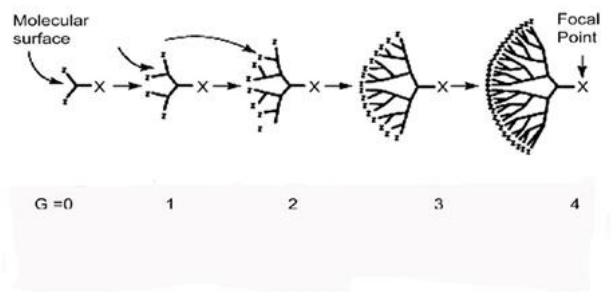


Figure 3: The Convergent Growth Method[28]