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Dendrimer based nanotechnology

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1. INTRODUCTION

The word dendrimer comes from the Greek word "dendron" which means "tree", thus indicating its tree-shaped structure. They are highly branched, with many arms held on a central core, symmetric and three-dimensional. Synthesis includes two major strategies: in the first one (divergent method) which was introduced by Tomalia and colleagues, synthesis begins from the core. Then synthetic or natural substrates are added according to several rules. In the second strategy (convergent method) Hawker and Frechet began the synthesis from what will become the surface of the dendrimer and proceeded to the core. Both methods include a multi-step polymerisation process. In each step, a layer of monomeric molecules is added and the number of layers defines the generation of the dendrimer. Their size is of nanoscale diameter (10-9 m) because of their controlled synthesis strategy.

Dendrimers are built from a series of branches around an inner core, providing products of different generations and offer intriguing possibilities in this regard. They can be synthesised from almost any core molecules and the branches similarly constructed from any bi-functional molecules (in our case lysine or ornithine), while the terminal groups can be modified chemically to achieve charged, hydrophilic, or hydrophobic surfaces. Their dimensions are extremely small, having diameters (depending on generation) in the range of 2 to 10 nm; that is they are authentic nanoparticles. Normal synthetic processes do not allow the growth of infinitely large dendrimers, usually because of steric problems. They can be synthesised starting from the central core and working toward the periphery (in divergent synthesis), or in a "top-down" approach starting from the outermost residues (in convergent synthesis), or built up from component dendrons, either by their covalent attachment or by their self-assembly. The series of lysine- and ornithine -based dendrons and dendrimers we have synthesised (by solid state procedures) and a widely studied PAMAM dendrimer is illustrated in Figure 1a. The largest we have studied has 64 amino groups at the surface, or if lipidic, 64 alkyl groups of various chain lengths (see Figure). Fréchet and colleagues have synthesized an amphipathic dendrimer, such a dendrimer has the propensity to self-associate. This ability to design the precise physicochemical character of the dendrons allows the formation of super-molecular assemblies, which in themselves can be interesting carriers for both drugs and genes.

Dendrimers can be made from a wide variety of biocompatible materials; the most frequently used are polyamidoamine (PAMAM), polyethylene oxide (PEO), polypropylene imine (PPI), polyethyleneimine (PEI), polyethylene glycol (PEG) etc3. Additionally dendrimers may be produced exclusively from

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amino acids. For example, lysine can be used as a trivalent core and a branching unit too.

Dendrimers are potential nanocarriers of agents because they are highly biocompatible and water soluble. Their solubility is related to the surface functional groups, their generation and even the core synthesis. Consequently, drugs that appear to have poor pharmacokinetic parameters, such as the hydrophobic ones, may be efficiently administered with these nanomolecules. Furthermore dendrimers show low toxicity and organ accumulation possibly due to the fact that drug release is achieved only near its target (e.g. a tumor). Another potential advantage that could be obtained by the use of this type of nanocarriers is the extended plasma half-life of the drug. Compared to linear polymers, dendrimers are more slowly excreted with the urine probably because of their decreased ability to filtrate through the renal glomerule4 whereas urinary clearance decreases with molecular weight. Beyond anatomical obstacles, they may also cross cellular barriers via transcellular or paracellular pathways by-passing some efflux transporters, such as P- glycoprotein (Pgp) or some drug metabolism enzymes like hepatic Cytochrome 450 (CYP450). It should be noted that efforts are being made so that the intracellular delivery of dendrimers can be controlled.

Huang and colleagues, created two Newkome-type dendrimers, differentiated over a varied alkyl spacer with guanidine end moieties. One of them could be delivered mainly in the cytosole and the other in the nucleus. Two major approaches have been developed for the transport of these molecules to the desired site in the body. The first one includes encapsulation of the drug into the cavities of the dendrimer. The encapsulated molecule is non-covalently attached via ionic, hydrogen bonds, Van der Waals or hydrophobic interactions. Thus the drug is safely carried because interactions with molecules of its environment, that could eliminate it or affect its pharmacokinetic parameters, are avoided. It has been observed (at PAMAM dendrimers) that pH modulates drug solubility and release by affecting the ionisation condition of the molecule. For example acidic drugs are protonated at relatively low pH and the opposite occurs when basic drugs are exposed to the same conditions. In addition, low pH promotes the protonation of the tertiary amines in the cavities of dendrimer, thus weakening the drug-dendrimer interactions. As a result drug release is favored. However, it has been reported that protonation of the administered molecule may enhance its hydrophobic interactions with the dendrimer cavities, as Gupta and colleagues demonstrated with studies on PPI dendrimers and hydrophobic drugs. Thus it could be assumed that both pH and the functional groups of the drug play a role in solubility enhancement. The second approach for drug delivery includes covalent conjugation of the drug to the dendrimer periphery. It permits a more efficient control of drug release and cell targeting as the administered molecule diffuses more slowly and allows interaction with specific interfaces. In some cases conjugation of increased amounts of several agents is precluded because of the steric hindrance. For example in the case of quinolone this obstacle was overcome with the use of a glycine molecule. Glycine was firstly attached to the agent and then conjugated to the surface of a PEGylated carrier. On the contrary, high amounts of peripherally and covalently bound hydrophobic molecules may cause dendrimer aggregation.

Low polydispersity (e.g. the low distribution of molecular weights) of dendrimers allows reproducible pharmacokinetic pattern, whereas their multivalency permits the precise attachment of several molecules to their periphery. These molecules may serve as solubilising or targeting groups for a more efficient and precise distribution in the blood that will lack many of the adverse effects4. Furthermore, they may reduce toxicity caused by specific end groups at the periphery of the dendrimer. PEG is an exceptionally important modifying molecule18. Like other hydrophilic molecules, PEG reduces immunogenicity and uptake by the organs of the reticulo-endothelial system (RES). Furthermore, PEGylation increases biocompatibility of dendrimers and offers greater protection of the delivered drug, as it was observed in experiments with PAMAM dendrimers.

2. STRUCTURE

Dendrimers consist of a series of chemical shells built on a small core molecule. Each shell consists of two chemicals, always in the same order. This is much like a layer cake, where each layer consists of a cake-frosting pair. With dendrimers, each shell is called a generation and we can speak of G2.5, which, in our cake analogy, would consist of cake-frosting-cake-frosting-cake, with no frosting on the top cake layer.

Dendrimers are very much like ordinary organic molecules for the first three generations. They are small and floppy without much consistent or specific three-dimensional structure. By G4 they are beginning to become spherical and to take on a preferred three dimensional structure. By G5 they have a consistent and specific three dimensional structure. The surface of all full generations consists of multiple amines, while the surface of the half generations consists of multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components.

Dendrimers are branching molecules with the branching beginning at the core. Depending on the core, the dendrimer can start with 3 to 8 (or more) branches, with 3 and 4 being the most common number. Starting from the core, the dendrimer consists of long chains of atoms with a branch point about every half dozen atoms. At each branch point, the current chain of atoms becomes two

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chains of atoms. The molecular structure has the form of a tree with a great number of branches. The name "dendrimer" is derived from the ancient Greek word "dendron" (tree), and from the Greek suffix "-mer" (segment).

3. TYPES OF DENDRIMERS

In recent years, dendrimers with different designed functionalities have become objects of particular academic and practical interest because of their unique super branched architectures, high densities of peripheral functionalities, symmetrical shapes, and mono dispersity. Here, some of the dendrimers having different functionalities are briefly described along with their area of utilization.

3.1. Liquid crystalline dendrimers

They consist of mesogenic (liq. crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers. Functionalization of end group of carbosilane dendrimers with 36 mesogenic units, attached through a C-5 spacer, leads to liquid crystalline dendrimers that form broad smetic A phase in the temperature range of 17–130 ◦C. Boiko et al. claims that they have synthesized first photosensitive liquid crystalline dendrimer with terminal cinnamoyl groups. They have confirmed the structure and purity of this LC dendrimer by 1H NMR and GPC methods. It was shown that such a dendrimer, under UV irradiation, can undergo E-Z isomerization of the cinnamoyl groups and [2 + 2] photocycloaddition leading to the formation of a three-dimensional network.

3.2. Tecto dendrimers

Tecto-dendrimers are composed of a core dendrimer, which may or may not contain the therapeutic agent, surrounded by dendrimers. The surrounding dendrimers are of several types, each type designed to perform a function necessary to a smart therapeutic nano device. The Michigan Nanotechnology Institute for Medicine and Biological Sciences (M-NIMBS) are developing a tecto dendrimers which perform the following functions: diseased cell recognition, diagnosis of disease state, drug delivery, reporting location and reporting outcome of therapy. They have already made and tested functional dendrimers which perform each of these functions. Even after a many questions on the way they are planning to produce a smart therapeutic nano device for the diseased cell like a cancer cell or a cell infected with a virus.

3.3. Chiral dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Chiral, nonracemic dendrimer with well-defined stereochemistry is particularly interesting subclass, with potential applications in asymmetric catalysis and chiral molecular recognition.

3.4. PAMAMOS dendrimers

Radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomblike networks with nanoscopic PAMAM and OS domains.

3.5. Hybrid dendrimers

Hybrid dendrimers are combination of dendritic and linear polymers in hybrid block or graft copolymer forms. The small den - drimer segment coupled to multiple reactive chain ends provides an opportunity to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers.

3.6. Peptide dendrimers

Dendrimers having peptides on the surface of the traditional dendrimer framework and dendrimers incorporating amino acids as branching or core units are both defined as 'peptide dendrimers'. Also peptide dendrimers can be defined as macromolecules that contain peptide bonds in their structure. Because of biological and therapeutical relevance of peptide molecules, peptide dendrimers play an important role in diverse areas including cancer, antimicrobials, antiviral, central nervous system, analgesia, asthma, allergy and Ca+2 metabolism. On the basis of their ability to be taken up by cells, making peptides very useful for drug delivery. One more interesting application of peptide dendrimers is that can be used as contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and serodiagnosis.

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3.7. Glycodendrimers

The term 'glycodendrimers' is used to describe dendrimers that incorporate carbohydrates into their structures. Glycodendrimers can be classified as: (i) carbohydrate-coated; (ii) carbohydrate centered; and (iii) fully carbohydrate-based. Glycodendrimers have been used for a variety of biologically relevant applications such as, glycodendrimers with surface carbohydrate units have been used to study the protein–carbohydrate interactions that are in many intercellular recognition events. The accessibility of the sugars is an important consideration for glycodendrimers used effectively to evaluate protein– carbohydrate interactions. Like this, study of protein–carbohydrate interactions, incorporation into analytical devices, formulation of gels, targeting of MRI contrast agents, drugs and gene delivery systems are some of the areas where glycodendrimers are likely to be beneficial.

3.8. PAMAM dendrimer

Perhaps the family of dendrimers most investigated for drug delivery is the polyamidoamine (PAMAM) dendrimer. Many surface modified PAMAM dendrimers are non-immunogenic, water-soluble and possess terminal -modifiable amine functional groups for binding various targeting or guest molecules. PAMAM dendrimers generally displayconcentration- dependent toxicity and haemolysis. PAMAM dendrimers are hydrolytically degradable only under harsh conditions because of their amide backbones, and hydrolysis proceeds slowly at physiological temperatures. The internal cavities of PAMAM dendrimers can host metals or guest molecules because of the unique functional architecture, which contains tertiary amines and amide linkages. PAMAM dendrimers are generally prepared by divergent method and product up to generation 10 (G10) have been obtained. PAMAM dendrimers are the most extensively reported moiety for almost all existing applications of dendrimers.

4. SUMMARY

Although dendrimer drug delivery is in its infancy, it offers several attractive features. Dendrimers expect to be a potential polymer for biomedical, pharmaceutical and biopharmaceutical fields in the 21st century. Easily controllable features of dendrimers such as their size, shape, branching length, their surface functionality allow to modify the dendrimers as per the requirements, makes these compounds ideal carrier in many of the applications. Still toxicity problems may arise, but they will be resolved by modifying dendrimer structure. Future work is necessary to find out cost-effective synthesis strategies and the relationship between dendrimer and drug molecules for successful commercialization of this technology.

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