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Cascade Molecule: An Innovation in Nanotechnology: Review Article

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ABSTRACT

The concept of nanotechnology has been made a lot of revolution in the field of dentistry both in diagnostic and therapeutic aspects. Dendrimers are a type of nanoparticles that has given promising results in various dental applications. This article gives a comprehensive view about the structure, synthesis, properties and applications of dendrimers.

Key words: Dendrimers, diagnosis, therapeutics.

INTRODUCTION

In the early 1980's, Donald Tomalia and his co-workers discovered a hyperbranched, monodisperse, three-dimensional molecules which were called as "dendrimers". These artificial macromolecules derived its name from the Greek word "Dendron" meaning 'a tree'. The Latin word "arbour" which also means 'a tree' was used by the Newkome's group to describe dendrimers. Their complex structures produced in a repetitive sequence of chemical reactions gave the term "Cascade molecule".[8, 13]

Structure[1]

The physical and chemical properties of the dendrimers are greatly influenced by their structure. The dendrimers consists of three distinct units:

i) A central core unit.
ii) Generations / branches attached to the core.
iii) Terminal functional group attached to the outermost series of branches.

The molecular structure of lower generation dendrimers is asymmetric in shape whereas that of higher generations are globular in shape. The starbust effect in dendrimers is due to the densely packed structure which is formed as they extend out to the periphery, leading to lack of space when a critical branched state is reached.

Synthesis [1,8,11]

The dendrimers are synthesised by one of the following three methods:

i) Divergent method.
ii) Convergent method.
iii) Double exponential and mixed method.

Divergent method: In this method the dendrimers grow from the core molecule and extend peripherally (from inside to outside)

Convergent method

It is a two-step process in which the dendrimers grow from outside to inside.

Double exponential and Mixed method: It is the recent and advanced method of synthesising dendrimers. It involves both divergent and convergent methods.

Types[8, 9,13]

1. PAMAM [Poly (Amido amine)]: Synthesised by divergent method these are the commercially available dendrimers. These are the first synthesised dendrimers and are also called as 'Starbust' dendrimers. The core molecule used for the synthesis is ammonia. It has the properties of high solubility and reactivity.
2. PPI / POPAM [Poly (propylene amine)]: Diaminobutane is the core material used. It is used in material science and biology.
3. Chiral dendrimers.
4. Multilingual dendrimers: contains multiple copies of a particular functional group.
5. Tectodendrimers: smart therapeutic system which diagnose as well as treat the disease.
6. Hybrid dendrimers.
7. Amphiphilicdendrimers.
8. Peptide dendrimers: used for diagnostic purpose and vaccine delivery.
9. Frechet – type dendrimers: highly soluble dendrimers.
10. PAMAMOS [Poly (Amindoamine Organo silicon)]: Silicon containing commercial dendrimers.

Properties[2,10]

1. Monodispersity: Dendrimers have a well defined molecular structure of different sizes that can be specifically controlled during synthesis.
2. Polyvalent: The multivalency allows better interaction with biological targets since most of the molecular interactions occur through biological multivalent bonds. Dendrimers can react with multiple receivers at a time in the biological site of action.
3. Solubility: Dendrimers have high solubility in organic solvents which leads to rapid dissolution. The activity of hydrophobic molecules is enhanced when they are attached with these dendrimers because of high solubility in water. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester. A marked difference was also observed in chemical reactivity[2].
4. Biocompatibility: Dendrimers are tested before using them as drug carriers and has been found to have no toxicity, not immunogenic, has the ability to cross the intestinal barriers and remain in the circulation for a considerable period of time.
5. Drug interaction: Dendrimers are synthesised with the characterisation that enables them to effectively deliver various drugs to the biologically specific sites. Dendrimers interact with drug molecules physically by absorption on surface by electrostatic interactions or by conjugation with the surface groups for covalent bonding or by encapsulation of the drug into the cavities of the dendrimers[10].

Applications

Dendrimers are a unique group of nano particles which are highly suitable for an effective drug delivery, particularly in the cancer treatment. The nanoparticles possess several properties like unparalleled molecular uniformity, multifunctional surface and presence of internal cavities, which make them suitable for various high technology uses both in biomedical and industrial fields.

Diagnostic[2]

1. Cardiac testing: It is used as an invitro diagnostic tool to assess heart muscle damage.
2. Contrast agents: Used in Magnetic Resonance Imaging as a contrast agent.

Therapeutic[1,2,3]

1. Targeted delivery of drugs.
2. Sialodendrimers.
3. Photodynamic therapy.
4. Gene therapy.
5. Boron neutron capture therapy.

Targeted delivery of drugs[4,5,6, 14]

The unique property of dendrimers to form internal cavities enables them to be used as a tool for drug delivery. It ensures encapsulation of guest molecules in the macromolecule interior. Drugs can also be attached to the surface groups of the dendrimers. The property of high solubility and increased plasma circulation time helps the dendrimers to passively target drugs to solid tumours. The cytotoxicity of anticancer drugs can

be considerably reduced by conjugating dendrimers with those drugs. For example 5-Fluorouracil (5FU) which is a potent anticancer drug has high toxic effects but slow release of 5-FU conjugated with PAMAM dendrimers reduces 5FU toxicity.[2] Dendrimers are a unique group of nano particles which are highly suitable for an effective drug delivery, particularly in the cancer treatment.[6]

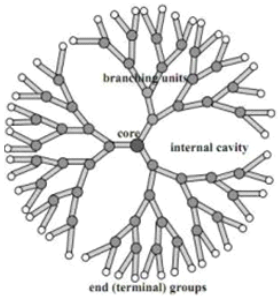

Fig.1: Structure of a dendrimer

Dendrimer-drug conjugates generally consist of an anti-neoplastic agent covalently attached to the peripheral groups of the dendrimer. These conjugates are more sensitive with increased bioavailability of the drugs. Few examples of anti-cancer drug and dendrimers conjugates are PAMAM-methotrexate conjugates, Paclitaxel- G4-PAMAM and Doxorubicin-G4-PAMAM.[4]

Sialodendrimers[2]

Influenza virus causes infection by the attachment of the virion to the cell membrane which is carried out by an interaction between the sialic acid groups on the cell surface and the virus receptor haemagglutinin. This attachment is prevented by the use of sialodendrimers that bind to the haemagglutinin.

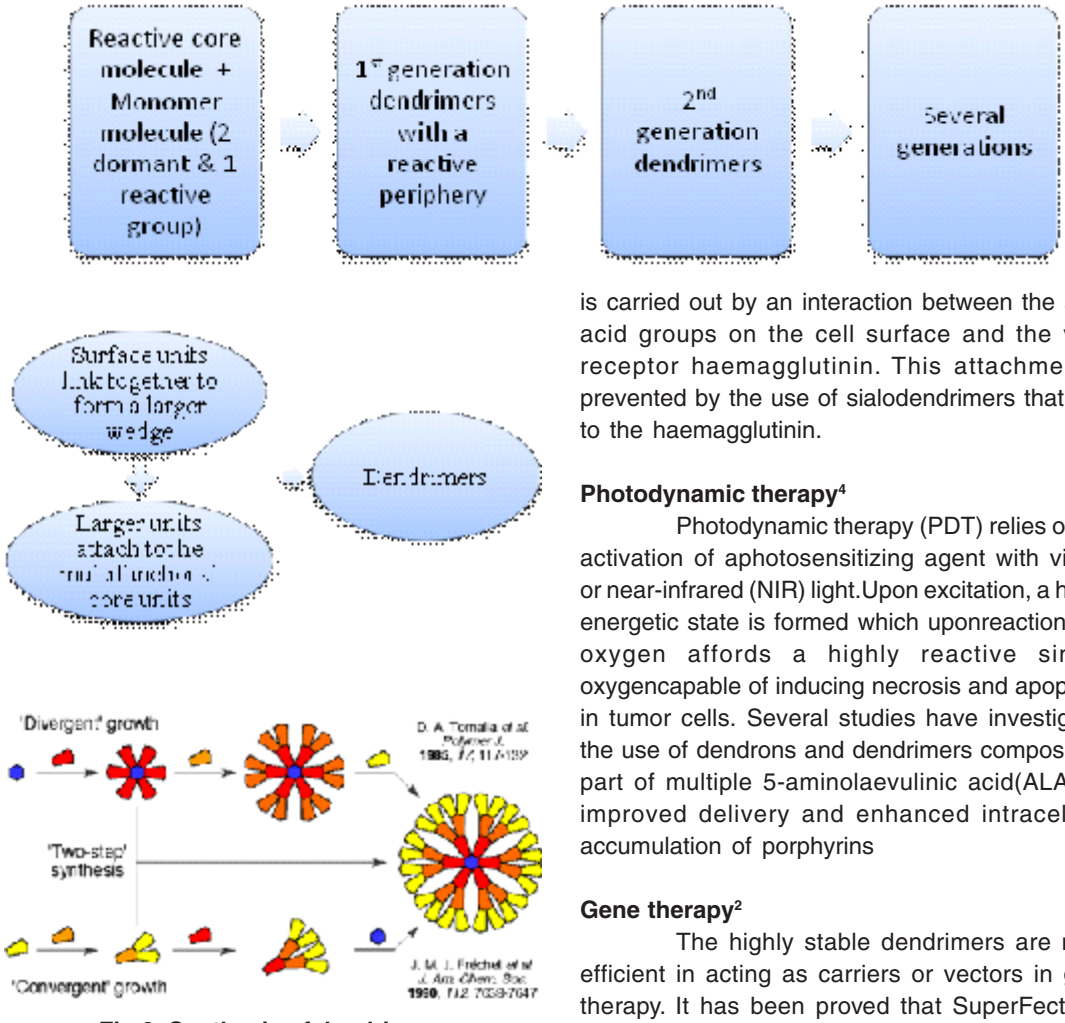

Fig.2: Synthesis of dendrimers

Photodynamic therapy[4]

Photodynamic therapy (PDT) relies on the activation of aphotosensitizing agent with visible or near-infrared (NIR) light.Upon excitation, a highly energetic state is formed which uponreaction with oxygen affords a highly reactive singlet oxygencapable of inducing necrosis and apoptosis in tumor cells. Several studies have investigated the use of dendrons and dendrimers composed in part of multiple 5-aminolaevulinic acid(ALA) for improved delivery and enhanced intracellular accumulation of porphyrins

Gene therapy[2]

The highly stable dendrimers are more efficient in acting as carriers or vectors in gene therapy. It has been proved that SuperFect™, a

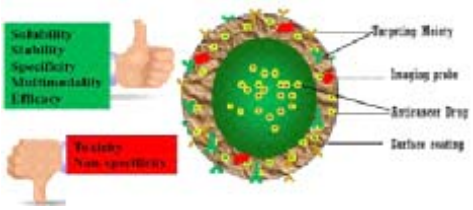

Fig. 3: Applications of dendrimers

commercially available activated dendrimers provide more efficient transport of DNA into the nucleus than liposomes.

Boron neutron capture therapy[2,3]

The boron isotope injected into the cancer patient gets concentrated in the cancer cells and the patient is then exposed to low-energy neutron beam. The reaction of these neutrons with the boron

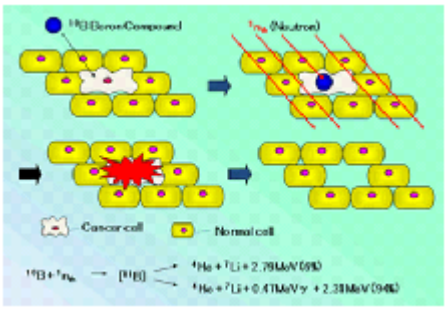

Fig. 4: Schematic process of BNCT

results in release of alpha particles that kills the cancer cells. Dendrimers are covalently attached to the boron isotopes to increase the number of boron atoms reaching the target cancer cells. Experimental results on this study have given positive results.

Other applications[1, 12]

1. Cosmetics: Dendrimers are used widely in the formulation of various cosmetics like nail polish, mascara, sprays, gels and lotions.
2. Water purification: Water contaminated with toxic metal ions or solutes can be purified with the addition of these dendritic polymers.[12]

Clinical trials [7,14]

- Malik et al.[7]synthesized conjugates of PAMAM dendrimers with cisplatin, a potent anti-cancer drug with nonspeciûc toxicity and poor solubility. The conjugates showed increased solubility, decreased systemic toxicity and enhanced permeation and retention (EPR) properties. Intravenous administration of these conjugates to mice bearing B16F10 tumors was able to selectively accumulate cisplatin in solid tumors (50-fold increase compared to that achieved after intra-venous administration of cisplatin at its maximum tolerated dose).
- Bhadraet al.[14] analysed the behavior of G4 PAMAM dendrimer/indomethacin complex (indomethacin, a nonsteroidal anti inûammatory drug) after intravenous administration. They obtained enhanced effective indomethacin concentrations (2.29 times) in the inûamed regions with the dendrimer/indomethacin complex when compared to the free drug in arthritic rats.
- Yang et al.[14] evaluated EGF as the targeting ligand in dendrimer-based targeting delivery systems.
- Therapeutic use of dendrimers-propranolol conjugate for reducing the effects of intestinal P-glycoprotein ondrug absorption could improve the oral bioavailability of propranolol and many other orally administrated drugs.
- Ketoprofen-PAMAM dendrimers complexes withsustained release behavior could be used as novelorally administrated formulations of NSAIDs.

Dendrimers have shown promising results in various biomedical applications. It is important for us to conduct more number of clinical trials using this advancement so as to use these nanoparticles more efficiently for the betterment of mankind.

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