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A FOCUS ON DENDRIMERS AS A NEW CONCEPT IN DRUG DELIVERY SYSTEM

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ABSTRACT:

The dendrimers represent a new class of macromolecular architecture and precise construction models as the emerging area of nano scale science and technology. Dendrimers based technologies provides existing new interfaces between chemistry, biology and advance materials. The article gives a concise review of dendrimers architecture, synthesis, properties and application. Dendrimers have successfully proved themselves as promising nano carriers for drug delivery because they can render drug molecules greater water solubility, bioavailability and biocompatibility. Nanoparticle drug delivery systems have advantage of increasing the selectivity and stability of therapeutic agent. Dendrimers are obtained with structural control approaching of traditional biomacromolecules such as DNA/RNA or proteins and are distinguished by their precise nanotechnology scaffolding and nanocontainer properties. Dendrimers have the ability to act as appropriate containers for delivery vehicles in vitro and in vivo due to their specific, precise and predictable custom designed dendritic polymer architecture. As such, these important properties are expected to play an important role in the emerging field of nanomedicine. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached i.e. conjugated or physically absorbed on to the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic application. Dendrimers provide a multivalent backbone for drug attachment and access to various new polymer architectures that are potentially relevant to drug delivery applications. Dendrimer targetting approaches improve the efficacy of drug therapy, thereby improving human health.

KEY WORDS: ***Dendrimers, nano carriers, biomacromolecule, nano medicine.***

INTRODUCTION:

The word Dendrimer originated from two words, the Greek word Dendron meaning tree and meros meaning part. Dendrimer is a polymer. Dendrimers synthesized from branch unit called monomers; it involves working on nano technology (based on nano scale which refers to 109 or a billionth of a meter or a millionth of a millimeter).[1] Current polymer molecules are long, spaghetti-like strands that grow in only two direction and dendrimer molecules grow three-dimensionally by a addition of shells of branched molecules to a centeral core, branched molecules are synthesized from Polyfunctional core (e.g. ammonia or ethylenediamine).[2] This branch 3D structure provides a high degree of versatility and surface functionality. Dendrimers consists three major architectural components-cores, branches and end groups [3].

HISTORY:

Father of dendrimers is Steve Edwards. Dendrimer chemistry was first introduced in 1978 by Fritz Voglte and coworkers; they synthesized first "cascade molecules"[4]. In 1985, Donald A. Tomalia synthesized the first family of Dendrimer at the same time, Newkeme's group independently reported synthesis of similar macromolecules. The term 'cascade molecule' is also used, but dendrimers is best established one. In 1990, Frichet, introduced the convergent approach to create dendrimers. In the early 1990's, Phenylacetylene dendrimers was created by Jefferey Moore using the convergent method [5].

STRUCTURE:

Nitrogen is a starting atom of dendrimer to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. Dendrimer consists of three architectural components namely:

(1) An interior core (core)

(2) Interior layers composed of repeating units, radically attached to the interior core (branches)[6]

(3) Exterior (terminal functionality) attached to the outermost interior generation (end groups)

TYPES OF DENDRIMERS:

(1) Pamam Dendrimers- PAMAM dendrimers are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. They are constructed using a reiterative sequence consisting of (a) a double Michael addition of methyl acrylate to a primary amine group followed by (b) amidation of the resulting carbomethoxy intermediate with a large excess of ethylenidiamine. [6]

(2) Pamamos Dendrimers- Radially layered poly (amidoamine-organosilican) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine interiors and hydrophobic organosilican exteriors.

(3) PPI Dendrimers- Poly (Propylene Amine) dendrimers were created by Meijer at DSM of the Netherlands. PPI dendrimers are synthesized by the divergent method starting from 1,4 diaminobutane. They are grown by a reiterative sequence consisting of (a) a double Michael addition of acrylonitrile to the primary amine group followed by (b) hydrogenation under pressure in the presence of Raney cobalt, [7] as an alternative name to PPI, POPAM is sometime use to describe this class of dendrimers.

(4) Polyether Dendrimers- In 1990, Frechet created this type of dendrimer by convergent approach. These dendrimers usually have carboxylic acid groups as surface groups serving as good anchoring point for further surface functionalization, and as polar surface groups to increase the solubility of the hydrophobic dendrimer types in polar solvents.

(5) Phenylacetylene Dendrimers- These dendrimer were created by Jeffry Moare in early 1990's by using convergent method.[7]

SYNTHESIS OF DENDRIMERS:

Dendrimers are generally prepared using either a divergent method or convergent one. In divergent method, dendrimer grows outwards from a multifunctional core molecule, the core molecules react with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimers[6].

Then the new periphery of molecules is activated for reaction with 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 dendrimer. The first synthesized dendrimers were polyamidoamines (PAMAMs). [8] They are also known starbust dendrimers, ammonia is used as the core molecule and in the presence of methanol, it reacts with methyl acrylate and then ethylenidiamine is added.

At the end of each branch there is a free amino group that can react with 2 methyl acrylate monomers and 2 ethylenediamine molecules. Each complete reaction sequence result in a new dendrimer generation.The number of reactive surface sites is doubled with every generation the mass increases more than twice.

The convergent method was developed as a response to weakness 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.[8]

PROPERTIES OF DENDRIMERS:

Dendrimers are monodisperse macromolecules, unlike linear polymers. The polymerization involved is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specially controlled during synthesis. Because of their molecular architecture, dendrimers show some significantly improved physically 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 which affects their rheological properties. Linear polymers have higher viscosity as compared to dendrimer solutions.[9] In contrast to linear polymers the intrinsic viscosity of dendrimer solutions does not increase linearly with mass but shows a maximum at a specified generation and then begins to decline.

For classical polymers the intrinsic viscosity increases continuously with molecular mass. Higher solubility, miscibility, and reactivity are due to the presence of many chain-ends in dendrimer. Dendrimer solubility is strongly influenced by the nature of surface groups. In nature tree-like structure have evolved to maximize the exposed surface area, e.g. to maximize the light exposure/number of leaves of a tree. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. The solubility of dendritic polyester was found remarkably higher with tetrahydrofuran (THF) as solvents then that of analogous linear polyester.[9] The presence of numerous terminal groups in dendrimers facilitates multiple simultaneous interactions of surface groups with the solvents, surfaces or other molecules and,

as a consequence, dendrimers tend to show high solubility, reactivity, and binding. Dendrimer 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 the macromolecule interior.

Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications8. Amine terminated PAMAM and Poly (Propylene Amine), cationic dendrimers that form cationic group at low pH are generally hemolytic and cytotoxic. Their toxicity is generationdependent and increases with the number of surface groups e.g. PAMAM dendrimer (generation 2, 3 & 4) interact with erythrocyte membrane proteins causing change in protein conformation. These changes increase with generation number and the concentration of dendrimers. Many potentional applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimer suitable for a variety of high technology uses including biomedical and industrial application [8].

APPLICATION:

Dendrimers have wide range of application since their surface, interior core can be easily tailored. Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavity [9]. These specific properties make dendrimers suitable for a variety of high technology uses .These are as follows:

(1) Dendrimers as targeted and controlled release drug delivery systems- Dendrimers can function as drug carriers either by encapsulating drug within the dendritic structure, or by inter-acting with drugs at their terminal functional groups by electrostatic or covalent bonds. Dendrimers are used as possible drug carriers because of their specific drug properties such as 3 dimensional structure, ability of many functional surface groups, their low polydispersity and their ability to mimic.[10]

(2) Dendrimers in AIDS therapy- Dendrimers can inhibit replication of human immunodeficiency virus by interfering with both virus adsorption and later steps (reversible transcriptase/integrase) in the virus replicative cycle. Polyanionic dendrimers were synthesized and evaluated for their antiviral effects. Phenyl dicarboxylic acid and naphthyl disulfonic acid dendrimers were found to inhibit the replication of human immunodeficiency virus type I (HIV-I; Strain III (B)) is MT-4 cells at a EC (50) of 0.1 and 0.3 Microg/ml, respectively. Dendrimers were non toxic to MT-4 cells up to the highest concentrations tested (250 Microg/ml).[10] These compounds were also effective against various other HIV –I strains, including clinical isolates, HIV-II strains, simian immunodeficiency virus(SIV,strain MAC (251)) and HIV-I strains that were resistant to reverse envelope glycoprotein gp 120 displayed reduced sensitivity to the dendrimers.

SPL 7013 has since been formulated into a vaginal gel (now called VivaGel) and developed under an investigational drug application to the U.S FDA as a way for women to prevent themselves from becoming infected with HIV during heterosexual intercourse.

(3) Dendrimers used in cancer treatment- A good example of such application is using dendrimers in boron neutron capture therapy (BNCT). Boron neutron capture therapy is an experimental approach to cancer treatment

which uses a two step process. First, a patient is injected with a nano-radioactive pharmaceutical which selectively migrates to cancer cell. This component contains a stable isotope of boron.[11]

Next, the patient is irradiated by a neutral beam of low energy or thermal neutrons. The neutrons react with the boron in the tumor to generate alpha particles, which destroy the tumor leaving normal cells unaffected. Dendrimers with covalently attached boron atoms have been prepared and first tests on these compounds have given positive results.

(4) Dendrimers used in gene therapy- Dendrimers can act as carrier, called vectors, in gene therapy. Vectors transfer gene through the cell membrane into the nucleus. PAMAM dendrimers have been tested as genetic material carriers, they are terminated in amino group which interact with phosphate groups of nucleic acids. This ensures consistent formation of transfection complexes. SuperFect-DNA complex (transfection reagent consisting of activated dendrimers) are characterized by high stability and provide more efficient transport of DNA into the nucleus then liposomes.[11] The high transfection efficiency of dendrimers may not only be due to their well-defined shape but may also be caused by the term pK of the amines (3.9 and 6.9).

(5) Dendrimer used as coating agent- Dendrimers can be used as coating agents to protect or deliver drugs to specific site in the body. E.g. PAMAM dendrimers after acetylation form conjugate with 5-fluorouracil (high toxic side effects) called dendrimer-5FU conjugates.The dendrimers are water soluble and hydrolysis of the conjugates release free 5-FU. The slow release reduces 5-FU toxicity. [10] Such dendrimers are useful carriers for antitumor drug.

(6) Dendrimer as solubilising enhancer- Dendrimers have a hydrophobic core and a hydrophilic surface layer and have been termed unimolecular micelles. Unlike traditional micelles, dendrimers do not have a critical micelle concentration. This characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure at all concentration of dendrimer [10].

A hydrophilic-hydrophobic core-shell dendrimers with PAMAM interior and long alkane chain exterior was shown to bind 5-fluorouracil, a water soluble antitumor drug. After phospholipid coating of the dendrimer-fatty-acid macromolecule, oral bioavailability in rats of 5-fluorouracil was nearly twice the level of free 5-fluorouracil [11].

(7) Dendrimers in preclinical studies- 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. Addition of contrast agents (paramagnetic metal cation) improves sensitivity and specificity of the method.

Dendrimers due to their properties are highly suited for use as image contrast media. Several groups have prepared dendrimers containing gadolinium ions chelated on the surface improves visualization of vascular structures in magnetic resonance angiography (MRA) of the body. It is a consequence of excellent signal-to-noise ratio [12].

(8) Dendrimer as Nano scale catalyst- The combination of high surface area and high solubility makes dendrimers useful as nano scale catalysts. They combine the advantages of homogenous and heterogeneous catalysts. Homogeneous catalysts are effective due to a good accessibility of active sites but they are often difficult to separate from the reaction stream. Heterogeneous catalysts are easy to separate from the reaction mixture but the kinetics of the reaction is limited by transport. All catalytic sites of dendrimers are always exposed towards the reaction mixture. They can be easily recovered from the reaction mixture by easily ultrafilteration methods.

The first example of catalytic dendrimer was described by the group of Van Koten. They terminated soluble polycarbosilane dendrimers in diamino arylnikel (II) complex.[12]

(9) Dendrimers in Photodynamic Therapy- The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes. Photosensitive dyes have been incorporated into dendrimers and utilized in PDT devices. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue. The possibility of improving the properties of dendrimers through appropriate unfunctionalization of their periphery makes dendrimers promising carriers for photosensitizers. ALA is a natural precursor of the photosensitizer protoporphyrin IX (PIX), and its administration is known to increase cellular concentrations of PIX [13].

(10) Dendrimers- based entry inhibitors of HSV infection- It has been seen that dendrimers are effective in protecting primary foreskin fibroblast cells in vitro from the cytopathic effects of HSV-I and inhibiting the early stages of viral replication. In the mouse HSV model, an intra vaginal dose of a representative dendrimer-SPL 2999, dissolved in saline (that is unformulated)-significantly protected mice from genital herpes infection and disease [14].

(11) Dendrimers in industrial process- Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. Cooper and co-workers synthesized fluorinated dendrimers, which are soluble in supercritical CO2 and can be used to extract strongly hydrophilic compounds from water into liquid CO2. This may help develop Technologies in which hazardous organic solvents are replaced by liquid CO2 [15].

CONCLUSION:

The extraordinary high level of synthetic control over the size, shape, surface functionality and interior void spaces makes the nanostructures ideal vectors for both passive and active drug delivery/diagnostic imaging applications. The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties such as high degree of branching, multivalency, globular architecture and well defined molecular weight. The ability to select nano scale sized vectors with mathematically determined number of surface groups and well defined interior void space allows systematic size adjustments to determine excretionary pathways while producing optimal ratios of targeting moieties, therapy and surface groups required in combination with desired solution behavior, excretionary pathway and acceptable toxicity margins. Dendrimers are useful tool for optimizing drug delivery of drugs having problems of poor solubility,

bioavailability and permeability. Recent success in simplifying and optimizing the synthesis of dendrimers provide a large variety of structure with reduced cost of their production. Finally, certain anionic surface-modified dendrimers are proving to function as safe and effective topical nano drugs against HIV and genital Herpes [17].

These dendrimer based nano pharmaceutics are in the final stages of human clinical testing in the U.S FDA approval process [16].There has been a considerable research progress in the field of dendrimers and the future should witness an increase in the number of commercialized dendrimer based drug delivery system.

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