Review Article

DENDRIMER- A NOVEL SCAFFOLD FOR DRUG DELIVERY

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ABSTRACT

A dendrimer described as a macromolecule characterized by its highly branched 3D structure which provides a high degree of surface functionality and versatility. Dendrimers also referred to as the "Polymers of the 21st century." Dendrimers components, namely (1) an initiator core (2) Interior layers (generations) composed of repeating units, radically attached to the interior core. (3) Exterior (terminal functionality) attached to the outermost interior generations. Examples: Poly(amidoamine)dendrimers(PAMAM), Radially layered poly(amidoamine-organosilicon) dendrimers(PAMAMOS), Propylene Imine dendrimers (PPI) etc. The properties of dendrimers are dominated by the functional groups on the molecular surface for example, a dendrimer can be water soluble when its end group like a carboxyl group. Possible to design a water soluble dendrimer with internal hydrophobicity, which would allow it to carry a hydrophobic drug in its interior. Volume of dendrimer increases when it has a positive charge. If this property can be applied, dendrimers can be used for drug delivery system (DDS) that can give medication to the affected part inside the patient's body directly. The major application of dendrimers are: Gene and oligonucleotide delivery, Targeting of anticancer chemotherapy, As anti-infective agent, In vivo diagnostics, Targeted and Controlled release drug delivery, In photodynamic therapy, In industrial processes etc. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

Keywords: Dendrimer, Radially layered poly(amidoamine-organosilicon), internal hydrophobicity, Targeted drug delivery, Controlled release drug delivery.

INTRODUCTION

In 1978, Fritz Vogtle and co-workers, introduced dendrimer chemistry[1] and in 1985, Donald A. Tomalia, synthesized the first family of dendrimers.[2] It is a highly branched synthetic polymer and consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped or generational structure with precise molecular weights, diameters in the 2 to 10 nm range size, its unique architectural design, high degree of branching, multivalency, globular structure and representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". Poor solubility, bioavailability, permeability, biocompatibility and toxicity can be overcome by dendrimers. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Dendritic polymers or dendrimers provide a route to create very well-defined nanostructures suitable for drug solubilization applications, delivery of oligonucletide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular.[3,4]

STRUCTURE

Dendrimers are built from a starting atom, such as nitrogen, after a repeating series of chemical reactions, carbon and other elements was added into it; produce a spherical branching structure. As the process repeats, result is a spherical macromolecular structure. Dendrimers possess three distinguished architectural components, namely a central core which is either a single atom or an atomic group, Generation in which branches emanating from the core composed of repeating units, which is radially in position and many terminal functional group generally located in the exterior of the macromolecule.[5,6] Structure of dendrimer as shown in (Fig. 1).

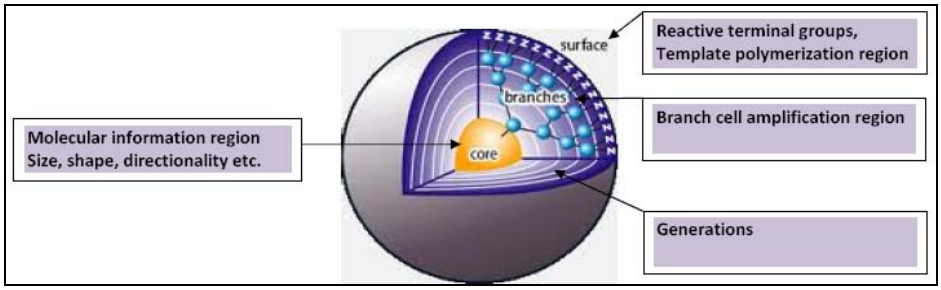

Figure 1: The Dendrimer Structure

Four main components are present in the dendrimer structure like Generation number is the number of focal points when going from the core towards the dendrimer surface, if dendrimer when going from the centre to the periphery having five focal points, is denoted as the 5th generation dendrimer. Between the focal points and the generation space, the homo-structural spatial segment is present that is Shell. The space between the last outer branching point and the surface known as outer shell, consists of a varying number of Pincers created by the last focal point before reaching the dendrimer surface. End group is also known as terminal group or surface group of the dendrimer, if dendrimers having amine end-groups are termed —amino-terminated dendrimers. [7,8]

ADVANTAGES OF DENDRIMERS

Dendrimers offers various advantages over other polymers:

(1) Dendrimers have nanoscopic particle size range from 1 - 100 nm, which makes them less susceptible for reticulum endothelium uptake.

(2) They have lower polydispersity index, due to stringent control during synthesis. As the density of branches increases the outer most branches arrange themselves surrounding a lower density core in the form of spheres and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.

(3) Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.

(4) Dendrimers can be modified as stimuli responsive to release drug.

(5) Dendrimers might show an enhanced permeability and retention effect which allows them to target tumour cells more effectively than small molecules.

(6) They can be synthesized and designed for specific applications. Due to their feasible topology, functionality and dimensions, they are ideal drug delivery systems; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal. [9,10,11]

TYPES OF DENDRIMERS

(1) Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS)

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute, discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nano-lithography, electronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains. [12,13]

(2) Poly (amidoamine) dendrimers (PAMAM)

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. When looking at the structure of the high-generation in two-dimensions, star like pattern observed. They are commercially available as methanol solutions and in generation G 0-10 with 5 different core type and 10 functional surface groups. [14,15]

(3) Poly (Propylene Imine) dendrimers (PPI)

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary tris-propylene amines present in interior portion. It commercially available up to G5, and wide applications in material science as well as in biology. [16] PPI dendrimers are available as Astramol™.

(4) Chiral dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis. [17]

(5) Liquid crystalline dendrimers

A highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour. They consist of mesogenic (liq. crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers.

(6) Tecto dendrimer

Tecto Dendrimer are composed of a core dendrimer, perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

(7) Hybrid dendrimers

Hybrid dendrimers are hybrids (block or graft polymers) of dendritic and linear polymers. Obtained by complete monofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic self-organized lattices that are less readily available from other modified dendritic structures.

(8) Multilingual Dendrimers

Multilingual Dendrimers contains multiple copies of a particular functional group on the surface.

(9) Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

(10) Amphiphilic Dendrimers

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

(11) Peptide dendrimers

Multiple Antigen Peptide dendrimers is a dendron-like molecular construct, use in biological applications, *e.g.* vaccine and diagnostic research. Peptide dendrimers can be used as drug delivery, contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and sero diagnosis.[18]

(12) Frechet-Type Dendrimers

Frechet-Type Dendrimers have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalisation, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media[19,20].

SYNTHESIS OF DENDRIMER

Mainly four methods are present for synthesis of dendrimers:

(1) Divergent growth method

This method was introduced by Tomalia. In this method growth of dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained. By this approach the first synthesized dendrimers were polyamidoamines (PAMAMs), also known as starbust dendrimers[21].

(2) Convergent Dendrimer Growth

Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.[22]

(3) Double Exponential and Mixed Growth

In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.[21,22]

(4) Hypercores and Branched Monomers growth

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields.

ENCAPSULATION OF DRUGS WITHIN THE DENDRITIC ARCHITECTURE

Dendritic architecture (open nature) has led several groups to investigate the possibility of encapsulating drug molecules within the branches of a dendrimer. This offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability and controlling its release. The nature of drug encapsulation within a dendrimer may be simple physical entrapment, or can involve non-bonding interactions with specific structures within the Dendrimer.[23-25]

(1) Unimolecular micelles

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. For example synthesised a symmetrical, four directional saturated hydrocarbon cascade polymer containing 36 carboxylic acid moieties with a neopentyl core. It was shown that lipophilic probes were located within the lipophilic infrastructure of the dendritic structures and it was concluded that the polymers exist as single molecules capable of molecular inclusion and therefore act as unimolecular micelles.[26-29]

(2) PEGylated dendrimers

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer to provide a hydrophilic shell around a hydrophobic dendritic core to form a unimolecular micelle. Because of its high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications. Liu et al., pentanol-based monomer was used to increase the flexibility and cavity size of the dendritic architecture by use of PEG.[30,31]

(3) Dendritic box

Jansen et al. described the synthesis of poly(propyleneimine) dendrimers based dendritic boxes. During the synthetic process, guest molecules could be entrapped within the cavities of the dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication. Through end group modification with a bulky amino acid derivative to yield a dense and rigid chiral shell with solid-phase properties and a flexible core capable of entrapping molecules[32,33].

(4) Cored dendrimers

Zimmerman and co-workers synthesised cored dendrimers that resemble hollow nanospheres,

encapsulate substances made them candidates for delivery vehicles. Encapsulation was achieved by post-synthetic modification of the dendritic architecture. The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups[34,35].

SURFACE INTERACTIONS BETWEEN DRUGS AND DENDRIMER

The external surfaces of dendrimers have been investigated as potential sites of interaction with drugs. Although the number of guest molecules incorporated into a dendrimer may be dependent to a limited extent on the architecture of a dendrimer, the loading capacity may be dramatically increased by the formation of a complex with the large number of groups on the dendrimer surface. The number of surface groups available for drug interactions doubles with each increasing generation of dendrimer.

(1) Electrostatic interaction between drug and Dendrimer

The presence of large numbers of ionisable groups on the surface of dendrimers provides an interesting opportunity for electrostatic attachment of numerous ionizable drugs, providing the resultant complex retains sufficient water solubility. For example electrostatic interaction can occur between PAMAM dendrimers and nonsteroidal anti-inflammatory drug ibuprofen. Electrostatic interaction can occur between the carboxyl groups of this weakly acidic drug and the amine groups of the dendrimers. It has been estimated that approximately 40 ibuprofen molecules interact with G4 PAMAM dendrimer at pH 10.5 causing a considerable enhancement of drug solubility[36].

(2) Conjugation of drug to dendrimer

The covalent attachment of drugs to the surface groups of dendrimers through hydrolysable or biodegradable linkages offers the opportunity for a greater control over drug release. Yang and Lopina have conjugated penicillin V (XII) with both G2.5 and G3 PAMAM dendrimers through a PEG spacer via amide and ester bonds, respectively. The use of an amide linkage provided bond stability, whereas ester linkage of the drug to the dendrimer provided a means of controlling drug release via hydrolysis. The microbial activity of the penicillin released by ester hydrolysis of the PEG-PAMAM (G3) conjugate was approximately the same (within 3%) as that of non-modified penicillin[37,38].

PROPERTIES AND CHARACTERIZATION OF DENDRITIC POLYMER

Properties of dendritic polymer

(1) Nanoscale sizes that have similar dimensions to important bio-building blocks, e.g., proteins, DNA.

(2) Lower generation anionic or neutral polar terminal surface groups show positive biocompatibility patterns as compared to higher generation neutral apolar and cationic surface groups.

(3) When dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) show non- or low-immunogenicity.

(4) Ability to arrange excretion mode from body, as a function of nanoscale diameter.

(5) An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties, reduces the drug toxicity and facilitates controlled release.

(6) Numbers of terminal surface groups suitable for bio-conjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.

(7) Surfaces that may be designed with functional groups to resist trans-cellular, epithelial or vascular bio permeability.

(8) Optimize biodistribution, receptor mediated targeting, therapy dosage or controlled release of drug from the interior space after the modification of surface groups.

(9) Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers.

(10) Dendrimers are monodisperse macromolecules. Size and molecular mass of dendrimers can be specifically controlled during classical polymerization process.

(11) In solution, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solution has significantly lower viscosity than linear polymers. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline.

(12) Dendrimers have some unique properties because of their globular shape and the presence of internal cavities, to encapsulate guest molecules in the macromolecule interior.

(13) The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Dendrimers solubility is strongly influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents[39,40].

METHODS FOR CHARACTERIZATION OF DENDRITIC POLYMER

Characterizations of dendrimer by various methods-

(A) Spectroscopy and spectrometry methods [41-46] most widely used for dendrimers Characterization like-

Nuclear Magnetic Resonance (NMR) Analysis in step by step synthesis of Dendrimer. To Probe the Size, Morphology and Dynamics of Dendrimers for organic dendrimers such as PPI etc.

Ultra-violet-visible spectroscopy (UV-VIS) Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units.

Infra red spectroscopy (IR) for routine analysis of the chemical transformations occurring at the surface of dendrimers.

Near infra red spectroscopy Used to characterize delocalize π-π stacking interaction between end groups of modified PANAM.

Fluorescence The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers.

Raman spectroscopy gave relevant information about the degree of cyclodehydrogenation of polyphenylene dendrimers, and the characterization of PPI and phosphorus dendrimers.

Mass spectroscopy Chemical ionization or fast atom bombardment can be used only for the characterization of small dendrimers whose mass is below 3000 Da. Electrospray ionization can be used for dendrimers able to form stable multicharged species.

X-ray diffraction (XRD) This technique should allow precise determination of the chemical composition, structure, size and shape of Dendrimer.

(B) Scattering techniques[47-50]

Small angle X-ray scattering (SAXS) gives information about their average radius of gyration (Rg) in solution. The intensity of the scattering as a function of angle also provides information on the arrangement of polymer segments, hence on the segment density distribution within the molecule.

Small angle neutron scattering (SANS) gives access to the radius of gyration, but may also reveal more accurate information than SAXS about the internal structure of the entire dendrimer. The location of the end groups has also been determined by SANS experiments conducted with PAMAM dendrimers and PPI dendrimers having labelled (deuterated) or unlabelled end groups.

Laser light scattering (LLS) to determine the hydrodynamic radius of dendrimers. Dynamic LLS is mainly used for the detection of aggregates.

(C) Microscopy methods[51,52]

Transmission microscopy Electron or light produce images that amplify the original, with a resolution ultimately limited by the wavelength of the source.

Scanning microscopy The image is produced by touch contact Q at a few angstroms of a sensitive canilever arm with sample. Ex. Atomic force microscopy.

(D) Size exclusive chromatography[53] allows the separation of molecules according to size.

(E) Electrical techniques[54-56]

Electron paramagnetic resonance (EPR) Quantitative determination of the substitution efficiency on the surface of PANAM dendrimers.

Electrochemistry gives information about the possibility of interaction of electroactive end groups.

Electrophoresis used for the assessment of purify and homogeneity of several type of water soluble dendrimers.

(F) Rheology and Physical properties[57-60]

Intrinsic viscosity used as analytical probe of the morphological structure of dendrimers.

Differential scanning calorimetry (DSC) used to detect the glass transition temperature which depends on thy moleculer weight, entangment and chain composition of polymers.

Dielectric spectroscopy (DS) Gives information about molecular dynamic processes (α-, β)

(G) Miscellaneous[61-63]

X-ray Photoelectron Spectroscopy (XPS) chemical composition of dendrimers such as poly (aryl ether) dendrons or PMMH dendrimers has been also obtained using XPS, even if this technique is most generally used for the characterization of layers.

Sedimentation for lactosylated PAMAM dendrimers, measurements of dipole moments for PMMH dendrimer.

Titrimetry to determine the number of NH_2 end groups of PAMAM dendrimers.

APPLICATION OF DENDRIMER

Specific properties such as unparalled molecular uniformity, multifunctional surface and presence of internal cavities makes dendrimers suitable for a variety of high technology uses and are as follows:

(A) Pharmaceutical application

(1) Dendrimer in ocular drug delivery[64,65]

PAMAM dendrimers with carboxylic or hydroxyl surface groups, improving residence time and enhance bioavailability of pilocarpine in the eye.

(2) Dendrimers in pulmonary drug delivery[66]

Positively charged PAMAM dendrimers (G2 and G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.

(3) Dendrimer in transdermal drug delivery[67,68]

Dendrimers are able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently due to its highly water soluble and biocompatible nature. For example improving the drug permeation through the skin when PAMAM dendrimer complex with NSAIDs like Ketoprofen, Diflunisal and

enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application.

(4) Dendrimer in oral drug delivery[69,70]

Oral drug delivery studies using the human colon adenocarcinoma cell line, which have indicated that low-generation PAMAM dendrimers cross cell membrane through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Increase in the cytotoxicity and permeation of dendrimers when increase in the concentration and generation.

(5) Dendrimers in targeted drug delivery[71]

Dendrimers have ideal properties which are useful in targeted drug-delivery system. For example PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively.

(6) Dendrimers for controlled release drug delivery[72]

Encapsulation of 5-fluorouracil into PAMAM dendrimers(G=4) modified with carboxy methyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity. Controlled release of the Flurbiprofen achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers.

(7) Dendrimers in gene delivery[73]

Dendrimers are extensively used as non-viral vector for gene delivery. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

(8) Dendrimer as solubility enhancer[74]

Dendrimers are unimolecular micellar nature, due to have hydrophilic exteriors and hydro-philic interiors and form covalent as well as non-covalent complexes with drug molecules and hydrophobes, and enhance its solubilisation behaviour.

(9) Cellular delivery using dendrimer carrier[75]

PAMAM dendrimers with lauryl chains to reduce toxicity and enhance cellular uptake, for example Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells.

(10) Dendrimers as Nano-Drugs [76]

Dendrimers as Nano-Drugs, useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs) when Poly(lysine) dendrimers modified with sulfonated naphthyl groups. Show potent antibacterial biocides against Gram positive and Gram negative bacteria when PPI dendrimers with tertiary alkyl ammonium groups attached to the surface and Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications.

(11) Dendrimers as bio mimetic artificial proteins[77,78]

Dendrimers are often referred to as “artificial proteins” due to their dimensional length scaling, narrow size distribution, and other bio mimetic properties. For examples PAMAM family, they closely match the sizes and contours of many important proteins and bio assemblies like insulin (3 nm), cytochrome C (4 nm), and haemoglobin (5.5 nm) are approximately the same size and shape as ammonia-core PAMAM dendrimers generations 3, 4 and 5, respectively. Generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes (form stable complexes with histone clusters to condense and store DNAwithin the nucleosome of cells.) and generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of biological cells.

(12) Dendrimers as nano-scaffolds[79,80]

Reducing the interaction with macromolecules from the body defense system, and imaging tags due to an excellent platform provided for the attachment of cell-specific ligands, solubility modifiers, and stealth molecules by dendrimer surface. For examples folate–PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron-capture treatment of cancer tumors.

(B) Therapeutic application

(1) Dendrimers in photodynamic therapy (PDT) [81]

Cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue. For example The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes.

(2) Dendrimers for boron neutron capture therapy (BNCT) [82]

The radiation energy generated from the capture reaction of low-energy thermal neutrons by 10B atoms has been used successfully for the selective destruction of tissue. Due to their well defined structure and multivalency, Dendrimers are a very fascinating compound for use as boron carriers.

(C) Diagnostic application

(1) Dendrimers as molecular probes [83]

Due to their distinct morphology and unique characteristics, use as molecular probes. For Example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular probe, because of their large surface area and high density of surface functionalities.

(2) Dendrimers as X-ray contrast agents [84,85]

Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin are used to obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary etc.

(3) Dendrimers as MRI contrast agents [86,87]

Introduction of target specific moieties to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer contrast agents, for example folate conjugated Gd (III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

(D) Dendritic Catalysts / Enzymes [88,89]

Dendrimers useful as nanoscale catalysts due to its combination of high surface area and high solubility. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture and by easy ultra filtration methods, can be recovered from the reaction mixture. Dendritic shells can be used to create a microenvironment which is favorable for catalysis or provide shielding for functional groups at the dendritic core.

(E) Industrial Processes [22]

Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. For example, fluorinated dendrimers, which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from, water into liquid CO_2. This may help develop Technologies in which hazardous organic solvents are replaced by liquid CO_2.

(F) Current and Potential Applications of Dendrimers [90,91]

- One dendrimer molecule has hundreds of possible sites to couple to an active species. This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side affects of medications on healthy cells.
- Modification of cell-cell interactions and gene expression (e.g.: alteration of transcription factors binding to DNA)
- New carrier system for drug delivery (gels, self-associating systems)
- Dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radio ligands, imaging agents, or pharmaceutically active compounds.
- Delivery of Nucleic acids, Encapsulated drugs and Covalently linked drugs.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.
- Vaccines against bacteria, viruses and parasites.
- Diagnostic reagents in: serodiagnosis (systems with surface ligands), Biosensor systems (systems containing dyes, reactive molecules) magnetic resonance imaging (e.g.: gadolinium adducts).

DENDRIMER BASED PRODUCTS [92-94]

Several dendrimer based products have already been approved by the FDA and some in Phase II clinical trials. Various dendrimer based products are –

(1) Alert ticket for Anthrax Detection

(2) Priofect™, Priostar™ and Starburst for targeted diagnostic, therapeutic delivery for cancer cells

(3) SuperFect for Gene Transfection

(4) Stratus CS for Cardiac Marker

(5) Vivagel for preventing HIV

CONCLUSION AND FUTURE PROSPECT

The main conclusion is that the high level of control over the architecture of dendrimer, their shape, branching length and density, and their surface functionality, makes dendrimer ideal carriers for the various applications like drug delivery, therapeutic and diagnostic agent. Poor solubility, bioavailability and permeability biocompatibility and toxicity can be overcome by use it. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Furthermore, the high density of surface groups allows attachment of targeting groups as well as groups that modify the solution behaviour or toxicity of dendrimers. Research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems. The biomedical applications of dendrimers clearly illustrate the potential of this new fourth architectural class of polymers and substantiate the high optimism for the future of dendrimers in this important field.

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