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REVIEW ARTICLE

Dendrimer: A Novel Polymer for Drug Delivery System

Takalkar PP*, Deshmukh VN, Sakarkar DM

Sudhakarrao Naik institute of Pharmacy, Pusad., Dist-Yavatmal,445204 (M.S.) India.

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ABSTRACT

Dendrimers are unique class of the polymer which is characterized by its extensively branched 3D structure that provides a high degree of surface functionality and versatility. Many drugs used in various therapies are facing difficulties like toxicity or nonspecific targeting. New delivery technologies could help to overcome this challenge. Nanostructures with uniform and well-defined particle size and shape are of eminent interest in biomedical applications because of their ability to cross cell membranes and to reduce the risk of premature clearance from the body. Hydrophobic drugs can be complex within the hydrophobic dendrimers interior to make them water-soluble or drugs can be covalently coupled onto the surface of the dendrimers. Structural features of this nanomolecule can be effectively modified for drug delivery in the field of pharmaceutical sciences and biotechnology. Present review deals with various applications along with relevant examples of dendrimers in brief.

KEYWORDS

Dendrimers, Nanostructures, Nanomolecule, Drug Delivery

INTRODUCTION

Development of highest bioavailable dosage form of a drug is always being challenge to the research scientist. Various approaches have been used to enhance the therapeutic effect of the drug with less toxicity as improvement of solubility, preparation of microspheres, microemulsion, liposomes etc. In the last decade, the field of preparation of materials with low dimensionality and the investigation of their properties gained more and more importance. Nanotechnology and chemistry has been applied on various platforms such as Targeted and controlled drug delivery, Medical devices, Cell/tissue engineering, Gene delivery, Molecular-tags, Biosensors, bioanalysis.[1,2] The field of dendrimers is a rapidly expanding area.

***Address for Correspondence:**
P. P. Takalkar
Sudhakarrao Naik institute of Pharmacy,
Pusad., Dist-Yavatmal,445204,
(M.S.), India.
E-Mail Id: pankajtakalkar87@gmail.com

Since Tomalia synthesized the first polyamidoamine (PAMAM) dendrimer in 1985, the growth in dendrimer research has increased almost exponentially. Initially efforts were concentrated on developing and adapting new and existing synthetic methods to provide the tools needed to expand this pioneering area of research. More recently attention has been directed toward the application and functional design of dendrimers including gene delivery systems to catalysts and catalyst support dendrimers can be found in materials chemistry, synthetic chemistry. Dendrimers, a nanoparticle based drug-delivery system have numerous applications in pharmaceuticals such as enhancing the solubility of poorly soluble drugs, enhancing the delivery of DNA and oligonucleotides, targeting drug at specific receptor site, and ability to act as carriers for the development of drug delivery systems. The therapeutic effectiveness of any drug is often diminished by its inability to gain access to the site of action in an appropriate dose. This is

often due to the poor solubility of the drug in the body's aqueous environment. Medicinal chemists initially attempted to address this problem by synthesizing a water-soluble derivative of the drug moiety. Unfortunately, even small structural changes can reduce the pharmacological activity of a drug. It is observed that dendrimers have "container" properties in the solution which makes them analogous to unimolecular micelles with the ability to maintain their structure stable at even higher concentrations of solvents Study of dendrimer mediated solubilization has been found to be superior to cyclodextrin mediated solubilization.[1-4]

What is a Dendrimer?

Dendrimer is a nanoparticle (10^{-9}) and so has advantages over microparticles or others due to its small size, easy uptake by cells (through endocytosis). They are branched macromolecules have a central core unit having a high degree of molecular uniformity, narrow molecular weight, distribution, specific size and shape characteristics, and a highly-functionalized, terminal surface.

Structure of Dendrimer

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. Structure of dendrimer as shown in (Fig. 1).[2,3]

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 center to the periphery having five focal points, is denoted as the 5th generation dendrimer.

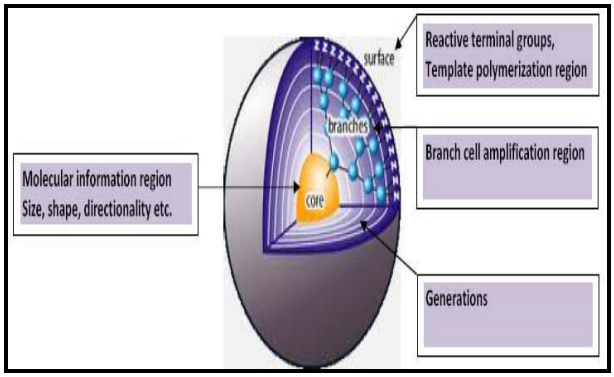

Figure1: Dendritic structure

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.[1-4]

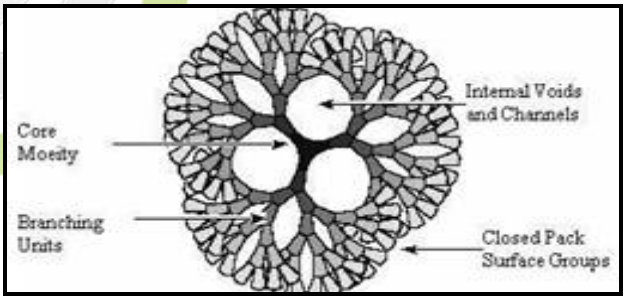

Figure 2: The Dendritic Structure

Properties of Dendrimer[6-8]

A) ***Monodispersity*:** well-defined molecular structure thus workable for a scalable size.

B) ***Nanoscale Size and Shape*:** The small size has a lot of advantages discussed later.

C) ***Polyvalency:*** i.e. the functional/reactive groups on the dendrimer structure. This responsible for more interactions between surfaces and bulk materials (adhesives, surface coatings, or polymer cross-linking). Example: topical vaginal microbicide called Vivagel.

D) ***Adaptive Nature of Dendrimers*:** Dendrimers can adapt "native" (e.g. tighter) or "denaturated" (e.g. extended) conformations dependent on the polarity, ionic strength and pH of the solvent.

Ideal Biocompatibility Properties[7]

a. Nontoxic

b. Non-immunogenic, biopermeable

c. Able to stay in circulation for the time needed to have a clinical effect

d. Able to target specific structure

Advantages of Dendrimers[2,7]

Dendrimers offers various advantages over other polymers:

- Dendrimers have nanoscopic particle size range from 1- 100 nm, which makes them less susceptible for reticulum endothelium uptake.
- 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.
- 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.
- Dendrimers can be modified as stimuli responsive to release drug.
- Dendrimers might show an enhanced permeability and retention effect which allows them to target tumour cells more effectively than small molecules.
- 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.[10,11]

Types of Dendrimers[1-5, 11, 12]

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 poly amidoamine (PAMAM) interiors and hydrophobic organo silicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, electronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honey comb like networks with nanoscopic PAMAM and OS domains.

Poly (amidoamine) Dendrimers (PAMAM)

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

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. PPI dendrimers are available as Astramol TM.

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.

Liquid crystalline dendrimers

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

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.

Hybrid Dendrimers

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

Multilingual Dendrimers

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

Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched poly phenylenes micelles.

Synthesis[1-5, 13, 14]

Two major strategies were reported for dendrimer synthesis. The first was called as “divergent method” in which dendrimer grows from core site. The second method was “convergent method” where number of dendrons reacts with multifunctional core to get a product. Another method was also introduced by Frechet and team called “double-stage convergent method” where divergent approach is followed by convergent assembly giving rise to orthogonally protected trimer.

Divergent Method

It is the strategy currently preferred. In this method, the core is reacted with 2 or more moles of reagent with at least 2 protecting branching sites followed by withdrawal of protecting groups. The liberated reactive site leads to first generation dendrimers .The process is repeated until desired size is obtained. The core may be either ethylene diamine or ammonia or cystamine. Initially alkylation of primary amines of core occurs with methyl acrylate followed by amidation of amplified ester groups with large excess of ethylene diamine. This produces series with primary amine terminal groups. Each amino group in turn reacts with 2 additional molecules of methyl methacrylate monomers followed by reaction with 2 or more ethylene diamine molecules to produce first generation dendrimers.[1]

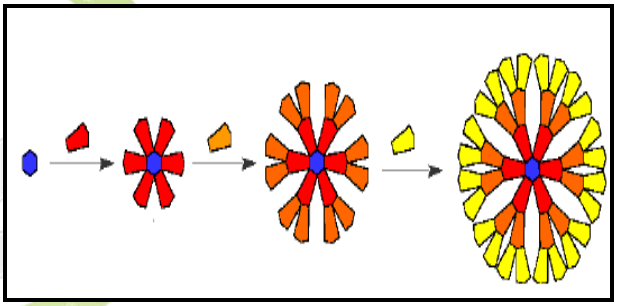

Figure 3: Divergent Growth Method

Convergent Method

Here growth of dendrimer starts at periphery with branching units and ends at the core by linking surface with more monomers. This strategy is limited to only lower generation dendrimers on account of nano scale stearic issues and low yields.[1]

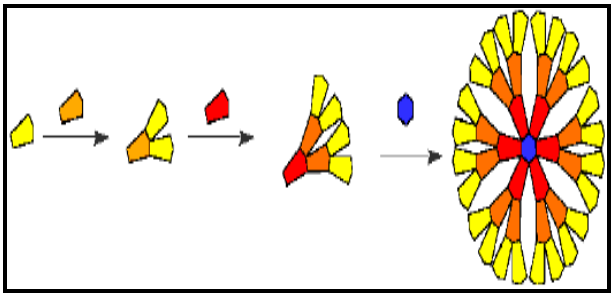

Figure 4: Convergent Growth Method

Hypercores' and 'Branched Monomers' Growth

Linkage of the oligomeric species in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation Dendrimers.[16]

Double Exponential' or Mixed Growth

The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of double exponential growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB2 monomer with orthogonal protecting groups for the A and B functionalities. This approach allows the preparation of monomers of both convergent and divergent growth from a single starting material.[15] These two products are reacted together to give an orthogonally protected timer, which may be used to repeat the growth process again. The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. The double exponential methodology provides a means whereby a dendritic fragment can be extended in either the convergent or divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcoming.[15,16]

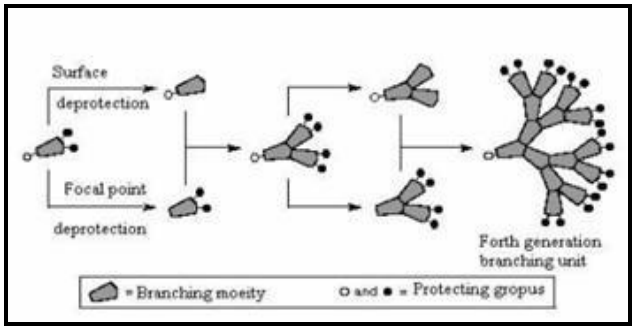

Figure 5: Double Exponential and Mixed Growth

Goals of Dendrimers

Drug delivery is very crucial aspect of formulation as its choice control bioavailability, concentration profile and side effects. Though most drugs are given in oral route, it must be stable in conditions like, enzyme activity. Thus a suitable DDS (Drug Delivery System) would protect drug against degradation which is satisfied by dendrimers.[4]

Goals of Dendrimers Include

- Modifying PK (Pharmacokinetic) & PD (Pharmacodynamic) properties of drug.
- Achieve controlled and targeted release of drug restricted to area desired.

Mechanism of Drug Delivery through Dendrimers

Dendrimers are particularly attractive as they offer a high drug-loading capacity. Two methods of dendrimer drug delivery are encapsulation of drugs and dendrimer –drug conjugates.[3,10]

A. Non-covalent Encapsulation of Drugs / Host –Guest Relation

Encapsulation of drugs uses the satiric bulk of the exterior of the dendrimer or Interactions between the dendrimer and drug to trap the drug inside the dendrimer.

B. Covalent Dendrimer–Drug Conjugates

In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids.

Applications of Dendrimers

A) *Pharmaceutical Application*

Dendrimers for Cancer Treatment

Millions of humans from all age groups are affected by the cancer. Most of the current chemotherapeutic agents on the market are the low molecular weight which makes them easily excreted, hence a higher concentration is

ultimately required, and additionally, these drugs when administrated alone, lack specificity and cause significant damage to noncancerous tissues. This results in serious, unwanted side effects.[19,20]

Dendrimers for Ocular Delivery

Dendrimers are especially ideal for synthesizing hydrogels and are more similar to living tissue than any other synthetic compound. By adding polyethylene glycol or PEG groups to the dendrimers, these hydrogels have applications including cartilage tissue production and for sealing ophthalmic injuries. These compounds can be utilized to control the release of dendrimers.[21,22]

Dendrimers for Oral Delivery

Oral drug-delivery system has been the dominant route for many years because of its significant advantages. It is by far the most convenient administration route with good patient compliance, especially in the patient's opinions. Along with these benefits, there are also some defects of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes. Transport of dendrimers throughout epithelial part of gastrointestinal tract depends upon its characteristics. Packaging a drug in a dendrimer host not only makes it soluble but also allows it to bypass the transporter protein that would normally stop it from being absorbed in the intestines after it has been taken orally.[22,23]

Dendrimers for Transdermal Delivery

Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. Stratum corneum acts as a major barrier for most of the drugs. PAMAM dendrimer complex with drugs could be improving the drug permeation through the skin as penetration enhancers.[24-25]

Dendrimers for Pulmonary Delivery

Pegylated dendrimeric micelles prolong the half-life of low molecular weight heparin (LMWH), Enoxaparin and increase the drug's pulmonary absorption, thereby efficacious in preventing deep vein thrombosis (DVT) in a rodent model. ShuhuaBai have prepared dendrimers of LMWH entrapped in PEG these produced a significant increase in pulmonary absorption and the relative bioavailability of the formulation was 60.6% compared to subcutaneous LMWH. The half-life of the PEG–dendrimer-based formulation was 11.9 h, which is 2.4-fold greater than the half-life of LMWH in a saline control formulation. When the formulation was administered at 48-h intervals, the efficacy of LMWH encapsulated in pegylated dendrimers in reducing thrombus weight in a rodent model was very similar to that of subcutaneous LMWH administered at 24-h intervals.[22,26]

Dendrimers for Targeted Delivery

Dendrimers have ideal properties which are useful in targeted drug-delivery system. The targeted delivery of chemotherapeutics to tumor cells reduced side effects compared to systemic delivery. Macromolecular delivery of anti-cancer drugs using multifunctional dendritic architectures allows for the conjugation of both drugs and targeting moieties such as folic acid, monoclonal antibodies, and peptides to the dendrimer periphery for increasingly specific delivery. The two general strategies of targeting include the passive targeting of bulk cancerous tissue and the active targeting of unique tumor cells.[22]

Non-specific or passive targeting of tumors is achieved by increasing the hydrodynamic radius of the dendrimer though Pegylation, leading to the accumulation of dendrimer in tumor tissue via the enhanced permeability retention (EPR) effect.[1-4,26]

Dendrimers for Bacterial and Viral Infection

Sialylated dendrimers, called sialo dendrimers, have been used to treat influenza infection. The first step in the infection of a cell by influenza virus is the attachment of the virion to the cell membrane. The attachment occurs through the interaction of a virus receptor haemagglutinin with sialic acid groups presented on the surface of the cell. Sialo dendrimers bind to

haemagglutinin and thus prevent the attachment of the virus to cells. Attaching sialinic acid moieties to the dendrimer surface enhances the therapeutic effect and allows the dendrimer to attain a higher activity in inhibiting influenza infection. A larger effect occurs with an increase in the number of sialinic acid groups.[26,27]

Poly (lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs). This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities. The general mode of action of antibacterial dendrimers is to adhere to and damage the anionic bacterial membrane, causing bacterial lysis. PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be potent antibacterial biocides against Gram positive and Gram negative bacteria. The nature of the counter ion is important, as tetra-alkyl ammonium bromides were found to be more potent antibacterials over the corresponding chlorides. Poly (lysine) dendrimers with mannosyl surface groups are effective inhibitors of the adhesion of E. coli to horse blood cells in a haemagglutination assay, making these structures promising antibacterial agents. Triazine-based antibiotics were loaded into dendrimers beads at high yields. The release of the antibiotic compounds from a single bead was sufficient to give a clear inhibition effect. Michelle K. Calabretta et al., investigated amino-terminated G5 PAMAM dendrimers are effective antimicrobial agents against common Gram-negative and Gram-positive pathogens P. aeruginosa and Staphylococcus aureus. Although unmodified, amino-terminated PAMAM is toxic to Human Corneal Epithelial Cells, partial coating of the dendrimers with PEG reduces cytotoxicity. The partial PEG coating maintains a high toxicity to the Gram-negative pseudomonal species, although it results in a large decrease in toxicity to Gram-positive staphylococcal species. These findings show that PAMAM derivatives could be an excellent candidate for a new class of antimicrobial compounds that could be incorporated to contact lenses to combat pseudomonal keratitis.[26,27]

Dendrimers for Controlled Release Drug Delivery

Encapsulation of 5-fluorouracil into PAMAM dendrimers (G=4) modified with carboxy methyl PEG5000surface 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 generation4 (G4) PAMAM Dendrimers.[22,28]

Dendrimer as Solubility Enhancer

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers having a hydrophobic core and a hydrophilic surface layer, 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 concentrations of dendrimer. A hydrophilic–hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-flurouracil, a water-soluble anti-tumor drug. After phospholipid coating of the dendrimer–fatty- acid macromolecule, oral bioavailability in rats of 5-flurouracil was nearly twice the level of free 5-flurouracil. Dendrimer based carriers could offer the opportunity to enhance the oral bioavailability of problematic drugs. Propranolol, conjugated to surfacemodifiedG3 PAMAM dendrimer, the solubility of propranolol increased by over two orders of magnitude. Thus, dendrimer nanocarriers offer the potential to enhance the

bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.[22,29,30]

Dendrimers in Gene Transfection

Dendrimers can act as vectors, in gene therapy. Amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus. Dendrimers of high structural flexibility and partially degraded high- generation dendrimers (i.e., hyper branched architectures) appear to be better suited for certain gene delivery operations due to their enhanced flexibility, which allows the formation of more compact complexes with DNA. It has been found that maximum transfection efficiency is obtained with a net positive charge on the complexes (i.e., an excess of primary amines over DNA phosphates).[23,31]

Cellular delivery using Dendrimer Carrier

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 (1hr versus > 3hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells.[2,30]

Dendrimers as Bio Mimetic Artificial Proteins

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 2dendrimer matches the width (2.4 nm) of DNA duplexes (form stable complexes with histone clusters to condense and store DNA within 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.[32,33]

Dendrimers as Nano-scaffolds

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.[23, 26]

B) Therapeutic Application

Dendrimers in Photodynamic Therapy (PDT)

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.[25,28,34]

Dendrimers for Boron Neutron Capture Therapy

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.[28,34]

C) Diagnostic Application

Dendrimers as Molecular Probes

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.[28,35,36]

Dendrimers as X-ray Contrast Agents

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.[35,36]

Dendrimers as Imaging Agent

Paramagnetic metal chelates such as Gd(III)-N, NV, NW, Nj-tetracarboxymethyl-1, 4, 7, 10-tetraazacyclododecane (Gd (III)-DOTA), Gd(III)-diethylene triamine penta acetic acid (Gd(III)-DTPA), and their derivatives increase the relaxation rate of surrounding water protons and are used as contrast agents for magnetic resonance imaging (MRI) However, shortcomings of these low molecular weight contrast agents are short circulation times within the body and inefficient discrimination between diseased and normal tissues. Lauterbur, Wiener and Tomalia pioneered the use of dendrimer-based MRI contrast agents by reporting some of the highest known relaxivities for these agents. These extraordinary properties have been studied extensively in vivo during the last decade by Kobayashi and Brechbiel. These properties appear to result from a combination of the geometrical amplification of chelated gadolinium that is possible on a dendrimers surface and higher rotational correlation times with minimal segmental motion that are intrinsic to these dendrimer conjugates. Consequently, dendrimer-based Gd(III) chelates consisting of generations 2 and 6 PAMAM dendrimers with 12 and 192 terminal surface amines conjugated to the chelating ligand 2-(4-isothiocyanatobenzyl)-6-methyl diethylene triamine penta acetic acid through a thiourea linkage were synthesized and used in vivo with rabbits. These contrast agents exhibited excellent MRI images of blood vessels upon intravenous injection. The blood circulation times were sufficiently long, with more than 100 min for large dendrimer conjugates such as the G = 6 PAMAM-TU-Gd(III) - DTPA.[36,37]

Dendrimers as MRI Contrast Agents

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.[36]

D) Tissue Engineering (Te) Applications of Dendrimers

The use of dendrimers' architectures in cells and TE applications is still in its infancy. Ligand-modified dendrimers have been proposed for use as substratum for cell culture and high performance bioartificial organs. Dendrimers are used in bone, cartilage tissue engineering.[23,36]

E) Dendritic Catalysts / Enzyme

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.[36,38]

F) Industrial Processes

Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within the irinterior. For example, fluorinated dendrimers, which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from, water into liquidCO_2. This may help develop Technologies in which hazardous organic solvents are replaced by liquid CO_2.[38,39]

G) Current and Potential Applications of Dendrimers

- 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 effects 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).[11, 23, 35, 38, 39]

Recent Advances of Dendritic Polymers

Targeting Dendrimers to HIV Infected Macrophages in vitro

Monocytes and macrophages disseminate HIV throughout body and targeting of these cells treat HIV. Tuftsin is a macrophage activator tetra peptide which bind specifically to monocytes and macrophages .In his work Dutta et al. prepared efavirenz (EFV) loaded, tuftsin conjugated fifth generation PPI to study their anti-HIV activity *in-vitro*. Entrapment of EFV in polymer was found to be 0.87g of EFV per g of TuPPI with entrapment efficiency of 49%. Without tuftsin the entrapment efficiency is 37%. Increase in efficiency is due to increased functional group available for complexation.[3]

Plasmid & Doxorubicin Co-delivery Targeting to Tumour

PEGlylated PAMAM dendrimer with tumour targeting moiety (peptide HAMPRH (T7)) was used to deliver tumour necrosis factor related apoptosis inducing ligand & Doxorubicin, a common anticancer drug.[2]

Future Prospects of Dendrimers

Though very few pharmaceutical products having dendrimers are available in market, the dendrimer technology holds great potential adding value to pharmaceutical products.

Future Development Focuses on Following Aspects

a. Reducing cost of synthesis of dendrimers so as to be applied extensively in membranes &other fields.

b. Enlarging application of membranes from hyper branched polymers to the fields of resources and environment.

c. Exploiting new applications of dendritic polymers in other fields of membrane.[2,3,18]

Dendrimer Based Products[18]

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

- Alert ticket for Anthrax Detection.
- Priofect™, Priostar™ and Starburst for targeted.
- Diagnostic, therapeutic delivery for cancer cells.
- SuperFect for Gene Transfection.
- Stratus CS for Cardiac Marker.
- Vivagel for preventing HIV.

CONCLUSION

The main purpose of this review is to focus various valuable applications of dendrimers which can be platform for the development of optimized novel drug delivery systems. Dendrimers drug delivery is in its infancy, it offers several attractive features. This novel class of polymers and their derivatives exhibit unique physicochemical and biological properties, which have great potential for use in a variety of applications. It has greater

flexibility in design. High control over the branching length, shape and size allows modification according to delivery system, so these can serve as ideal carrier for drug and various other applications. We still do not know whether these synthetic polymers, once they entered the body can cause damage to other tissues. Even though toxicity problems if arise, they will be minimized by modifying dendrimer architecture. As the synthesis involves multistep process future work is necessary to find out cost effective synthesis strategies with minimum efforts and the relationship between dendrimer-drug molecules for effective commercial utilization of this technology.

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