Review Article

Poly (propylene imine) Dendrimer: Synthesis, characterization and applications in various drug delivery

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Received: 18 May 2020 Revised: 19 June 2020 Accepted: 28 June 2020

Abstract

Dendrimers are a novel class of macromolecule having highly repetitively branched molecules consists of a monomer unit. Dendrimer consists of a tree like shaped structure. Dendrimer composed of initial core, interior layers (generations) and exterior (terminal functional group). Types of dendrimers, examples: Poly (propylene imine) dendrimer (PPI), Poly (amidoamine) dendrimers (PAMAM), Radially layered Poly (amidoamine – organosilicon) dendrimers (PAMAMOS) etc. The properties of dendrimers are determined by monodispersity, size and shape, rheological property, crystallinity, immunogenicity and cytotoxicity. Synthesis of dendrimers is convergent method, divergent method and double exponential and mixed growth. The major applications of dendrimers are: Pharmaceutical applications, therapeutic applications, diagnostic applications, dendritic catalyst/enzyme, industrial process, and current and potential applications of dendrimers. This review focus on dendrimer structure, advantages, types, properties, characterization, synthesis, mechanism, other forms of dendrimers, applications of dendrimers and the mainly focus on PPI dendrimers.

***Keywords*:** Dendrimer, Poly (propylene imine) dendrimer, Poly (amidoamine) dendrimers, Poly (amidoamine – organosilicon) dendrimers, convergent, divergent

Introduction

The term dendrimer coined from the Greek word "Dendron" refers to a tree. The word for dendrimer is Arborols (from Latin word arbor conjointly which means a tree and cascade molecule. Dendrimers are repetitively branched molecules consists of a compound unit connected core, wherever a number one to a monodisperse tree like star formed having diameters with in the 2 to 10 nm vary. Dendrimer having high functionality and very low polydispersity. Dendron usually contains a single chemically addressable group called the focal points (branching points) (Sadhana et al., 2015).

There are various advantages of dendrimers described here that makes selections in different drug targeting:

- Dendrimers have nanoscopic particle size range from 1-100nm, which makes them less vulnerable for reticulum endothelium uptake.
- Due to rigorous control throughout synthesis, they have lower polydispersity Index. As the density of twigs growth, the outer most twigs arrange themselves surrounding an inferior density core with the sort of spheres and external surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.
- Many functional groups are present on exterior surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.
- Dendrimers can be altered as stimuli responsive to release drug.
- Dendrimers might show an improved permeability and retention effect which permits them to target tumor cells effectively than small molecules.
- They can be synthesized and designed for specific applications. Due to their possible topology, practically and dimensions, they're ideal drug delivery systems, and also, their size is extremely close to numerous necessary biological polymers and assemblies like DNA and proteins which as physiologically ideal (Patri et al., 2002; Morgenroth et al., 1997; Nanjwade et al., 2009; Garg et al., 2011).

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DOI: https://doi.org/10.31024/ajpp.2020.6.3.10

Structure of dendrimers

Dendrimers area unit made up of a beginning atom, like gas to that carbon and different components are added by a repeating series of chemical reactions that makes a spherical branching structure. As the process repeats, successive layers are adjoined, and the sphere can be expanded to the size needed by the investigator. The result is a spherical molecule structure whose size is associated likeness to simple protein and haemoglobin, however smaller than such multimers because the large immune globulin protein advanced (Figure 1).

Dendrimers consists of 3 distinguished architectural components:

a) An initial core.

b) Interior layers (generation) constitute of repeating units, basically attached to the interior core.

c) Exterior (terminal functional group) attached to the outermost interior generations, as shown above (Pushkar et al., 2006; Sakthivel and Florence, 2003; Cheng et al., 2008; Karanjavkaretal, 2016).

Components of Dendrimers

Generation

It is the hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points).

5th Generation Dendrimer

A dendrimer having five (5) focal points once moving from the centre towards the outer boundary is significance because the 5th generation dendrimer and abbreviated as G5-dendrimer.

Ex: A 5th generation polypropylene imine (PPI) is abbreviated to a G5-PPI dendrimer. The core of the dendrimer is typically selected as generation zero (G0) i.e. the core structure has no focal points, as hydrogen substituents are not considered as focal points. Intermediates shaped throughout the dendrimer synthesis are generally termed as half-generations.

Ex: The PAMAM dendrimers terminated with carboxylic acid.

Shell

The dendrimer shell is the generation space (i.e. the homo-structural spatial segment) between the focal points.

Outer shell: The house between the last outer branching purpose and also the surface is outer shell.

Inner shell: Dendrimer interior is inner shell.

Pincer

The outer shell of dendrimers contains a variable range of pincers shaped by the last focus point headed before the dendrimer surface. Due to the division in the chain of dendrimers at the focal points, the number of pincers in the polypropylene imine (PPI) and poly amido amine (PAMAM) dendrimers becomes half the number of the surface groups present. (because in these dendrimers the chain divides into 2 chains in every focal point).

End Groups: End groups are usually known as the surface cluster of the dendrimer or terminal cluster. Dendrimers terminated with amino alkane end-groups are named as amino-terminated dendrimers. Solubility of dendrimer in solvent rely on finish cluster (Pushkar et al., 2006; Sakthivel and Florence, 2003; Zimmerman and Lawless, 2001).

Types of dendrimers

Different types of dendrimers have been reported by various researchers as mentioned below (Cheng et al., 2008; Hawker and Frechet, 1990; Priya et al., 2013; Hari et al., 2012)(Table 1):

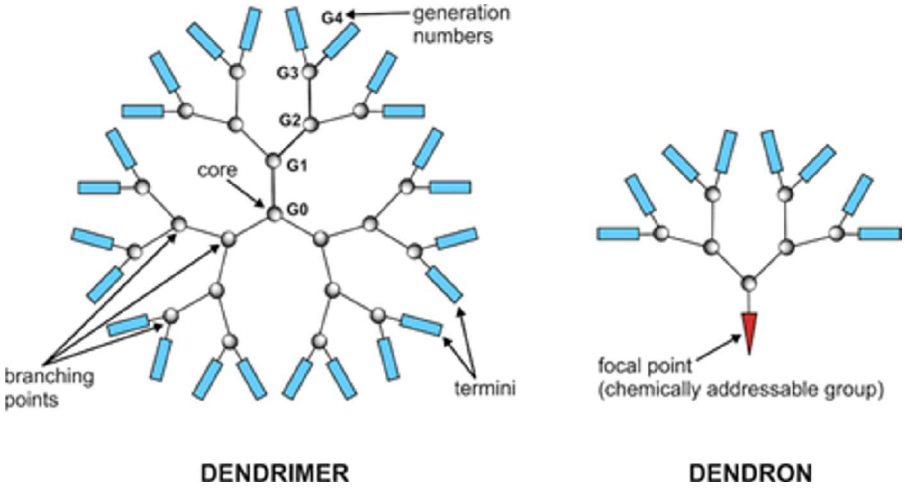

Figure 1. Structure of Dendrimer

- ✓ PPI Dendrimer
- ✓ PAMAM Dendrimer
- ✓ PAMAMOS Dendrimer
- ✓ Tecto Dendrimer
- ✓ Chiral Dendrimers
- ✓ Hybrid Dendrimers
- ✓ Liquid Crystalline Polymers
- ✓ Amphiphilic Dendrimers
- ✓ Micellar Dendrimers
- ✓ Multiple Antigen Peptide Dendrimers
- ✓ Frechet – Type Dendrimers
- ✓ Multilingual Dendrimers

Properties of dendrimers

Monodispersity

Dendrimer are monodisperse having same size. Dendrimer synthesis is specifically controlled that reduces size variation not like linear molecule synthesis produces random structure and high size variation (Garg et al., 2011; Trivedi et al., 2012; Kumar et al., 2011). Dendrimer synthesized from convergent technique having high monodispersity than alternative technique (Table 2).

Most of structural defect occur throughout formation of high generation dendrimer attributable to incomplete reaction, steric hindrance problem.

Table 1. Types of Dendrimers (Hari et al., 2012)

Types	Definition	Synthesis	Example	Applications
PAMAM (Poly amido amine) Dendrimer	It possesses amino groups on the surface.	Divergent	Dendritech ™ (USA)	Material science and Biomedicine computer toners
PAMAMOS (Radially layered poly amido amine organosilicon) Dendrimer	Inverted unimolecular micelles consists of hydrophilic nucleophilic polyamidoamine interiors and hydrophobic organosilicons (OS) exteriors.	Convergent and Divergent	SARSOX	Nano-lithography, Electronics, Photonics, Chemical catalysis precursor for honeycomb like network preparations.
PPI (Polypropylene Imine) Dendrimer	Poly-alkyl amines having primary amines as end groups and its interior consists of numerous tertiary trispropylene amines.	Divergent	Asramol by DSM (Netherlands)	Material science and Biology
Tecto Dendrimer	It is composed of a core dendrimer with multiple dendrimers at its periphery.	Divergent	Stratus®, CS Acute Care ™, Starburst®, Mercapto,	Diseased cell recognition, Diseased state drug delivery diagnosis, Reporting location to outcome of therapy.
Chiral Dendrimer	Chilarity is based on construction of constitutionally different but chemically similar branches to a chiral core.	Convergent	Chiral dendrimers derived from pentaerythritol.	Biomedical applications, Chiral catalyst.
Hybrid Dendrimer	It is a combination of dendritic and linear polymer in hybrid block or graft copolymer forms	Divergent	Hybrid dendritic linear polymer, Polysilsequioxanes	Biomedicals. Molecular electronics, Nanophotonics, Sensing
Amphiphilic Dendrimers	Unsymmetrical globular dendrimers built with two segregated sites of chain end.	Divergent	SuperFect, Hydra amphiphiles and Bola amphiphiles	Structure directing agent, use as polar part, cell and gene transfection.
Micellar Dendrimer	Unimolecular micelle structure of water soluble hyperbranched polyphenylene.	Divergent	Beclomethasone dipropionate, NX – 200, Magnevist®	Biological and medical applications, Drug delivery, Imaging agent.
Multiple antigen peptide Dendrimer	Dendron like molecular construct based upon a polylysine skeleton.	Convergent synthesis.	Viva Gel	Used in vaccines and diagnostic research, Biological applications.
Frechet type Dendrimers	Dendrimers having carboxylic acid groups as surface groups and containing poly benzyl ether hyper branched skeleton.	Convergent Synthesis.	Frechet type dendron azides, Priostar™.	Drug carrier, Purifiers, Organic synthesis, Detecting agents, Drug delivery.
Liquid crystalline Dendrimer	It consists of a mesogenic monomers.	Divergent	Mesogen functionalized carbosilane dendrimers	Science and Engineering
Metallo Dendrimers	Dendrimers with incorporated metal atoms.	Convergent	Zinc porphyrin dendrimers (M = Zn).	Sensing Catalytic applications, Mimic Biomolecules, Light harvesting, Biomarkers

Table 2. Properties of dendrimer and Linear Polymers*

S. No.	Property	Dendrimer	Linear Polymers
1	Structure	Compact, Globular	Not Compact
2	Synthesis	Careful & Stepwise growth	Single step polycondensation
3	Structural control	Very high	Low
4	Architecture	Regular	Irregular
5	Shape	Spherical	Random coil
6	Crystallinity	Non – crystalline, Amorphous materials lower glass temperatures.	Semi crystalline / crystalline materials higher glass temperatures.
7	Aqueous solubility	High	Low
8	Non polar solubility	High	Low
9	Viscosity	Nonlinear relationship with molecular weight	Linear relation with molecular weight
10	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydisperse

***References:** Duncan and Izzo,2005; Chen et al.,2004; Jevprasesphant et al.,2003; El-sayed et al., 2002; Fischer et al., 2003

Technique of Characterization for Monodispersity

- ✓ Mass Spectroscopy
- ✓ Size exclusion Chromatography
- ✓ High performance liquid chromatography
- ✓ Transmission electron microscopy
- ✓ Gel Electrophoresis

Solubility

Functional group present on the surface decide solubility of dendrimer. Hydrophilic cluster on surface is soluble in polar solvent like water. Hydrophobic group on surface are soluble in non-aqueous solvent.

Internal cavity carriers' hydrophobic drug and improves solubility. In a solubility check with tetrahydrofuran because the solvent, the solubility of nerve fiber polyester was found remarkably on top of that of analogous linear polyester.

Size and Shape

Size of dendrimer is in nanometer. Due to less particle size not solely, dendrimer simply cross the semipermeable membrane however conjointly clearance from body is reduced. Dendrimers show some considerably improved physical and chemical properties attributable to their molecular architecture, as compared to traditional linear polymers. Shape of dendrimer depend upon generation of dendrimer.

Lower generation

It has open planer elliptical shape.

Higher generation

It has compact spherical shape.

Rheological property

In solution linear chains exist as flexible coils, in contrast dendrimers from a tightly packed ball which influences its rheological properties. Dendrimer having less viscosity than the linear polymer type. As molecular mass increases intrinsic viscosity increases upto 4^{th} generation dendrimer then decreases.

Crystallinity

Dendrimer are non-crystalline and amorphous material.

Immunogenicity

Dendrimer surfaces changed with little useful teams or synthetic resin glycol (PEG) they become non-immunogenic or less immunogenic.

Cytotoxicity

Cytotoxicity of dendrimer rely on core of dendrimer however it conjointly tormented by useful cluster gift on surface of dendrimer having amino (-NH2) cluster at surface shows cytotoxic property but this conjointly rely on generation of dendrimer and concentration. Higher generation dendrimers has been reported as the most toxic.

Synthesis of dendrimers

Four methods are mainly used for synthesis of dendrimers (Svenson and Tomalia, 2012; Barbara and Maria, 2001). They are describe here:

Divergent growth method

This method was introduced by Tomalia. In this technique growth of dendrimers originates from a core website. 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 starburst dendrimers (Figure 2).

Convergent dendrimer growth

Convergent dendrimer growth begins at what's going to find yourself being the surface of the dendrimer, and works inwards by step by step linking surface units beside additional. When the growing wedges are large enough, several are attached to suitable core to give a complete dendrimer. Convergent growth methodology has many advantages like comparatively easy to purify the required product, occurrence of defects in the final structure is minimized, does not allow the formation of high generation dendrimer as a result of lipid issues occur within the reactions of the dendrons and also the core molecule (Figure 3).

Double exponential and mixed growth

In this approach two products (monomers for both divergent and convergent method) 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 a lot of refined than the power to create giant dendrimers in comparatively few steps.

Hypercores and branched monomers growth

This method involves the pre-assembly of oligomeric species which can be combined together to provide dendrimers in fewer steps or higher yields.

Mechanism of drug delivery through dendrimers

The well-defined 3D structure and lots of purposeful surface teams, drug molecules are often loaded each within the interior of the dendrimers in addition as connected to the surface teams. Dendrimers will perform as drug carriers either by encapsulating drug inside the nerve fiber structure, or by interacting with drugs at their terminal purposeful teams via static or valence bonds (prodrug) (Figure 4 and 5).

These are broadly classified into two mechanisms for drug delivery:

a) Drug molecules can be physically entrapped within the dendritic structure;

b) Drug molecules can be covalently linked into the dendrimer surface (or) other functionalities to produce dendrimer drug conjugates.A dendrimer of higher generations consists of shell. A shell consists of a central core and altering two layers of monomers around it. Amines represent the central core which can typically get replaced by sugar. All core molecules have multiple and identical reaction site. Amine is that the simplest core molecule present with three useful sites. The surface of all

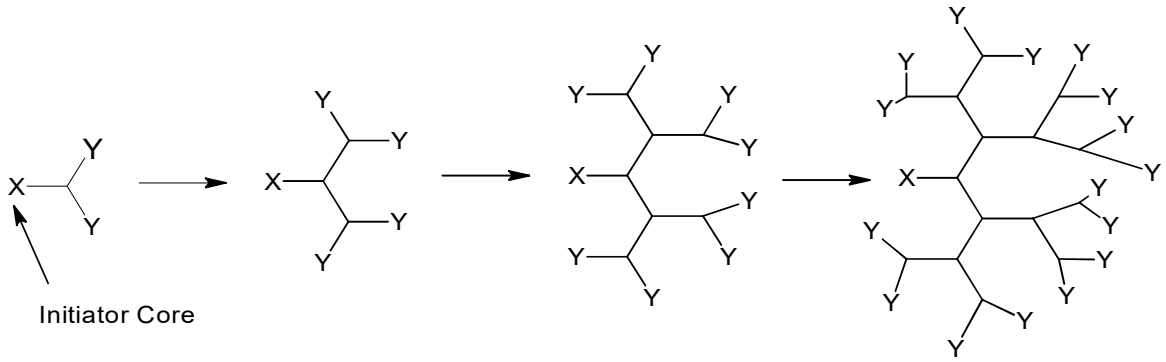

Figure 2. Synthesis of dendrimer by divergent method

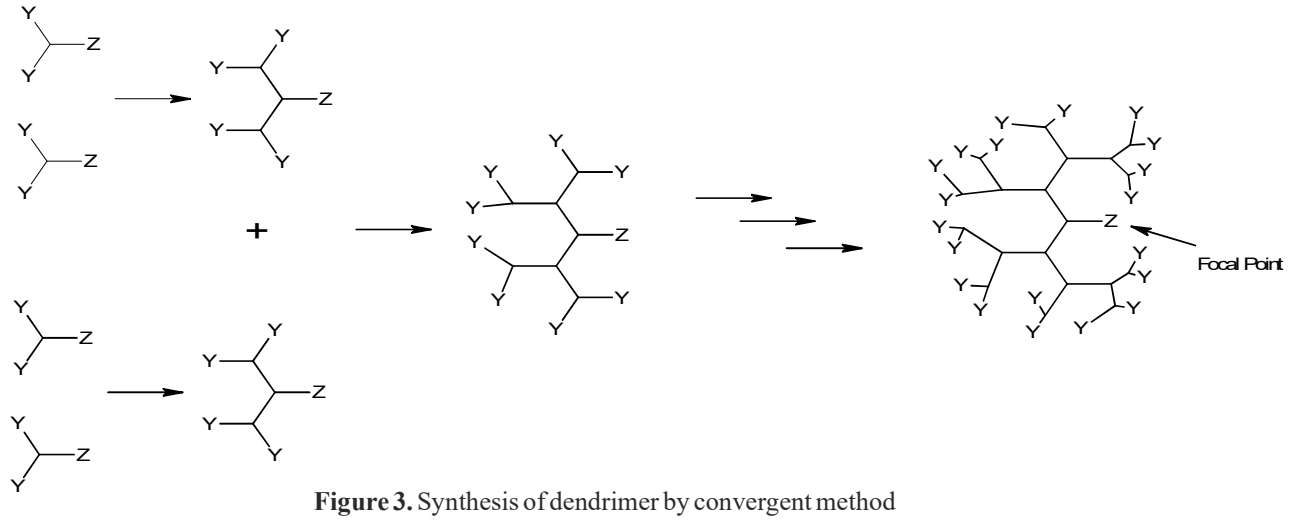

Figure 3. Synthesis of dendrimer by convergent method

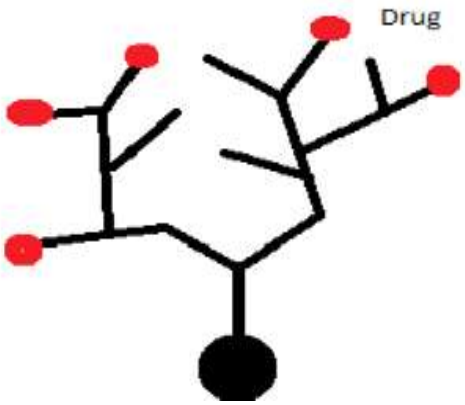

Figure 4. A dendrimer molecule with drug molecules loaded at terminal surface of branches

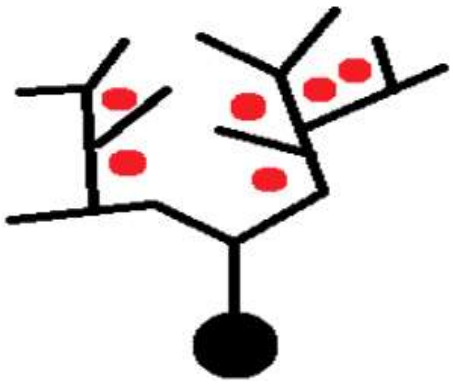

Figure 5. A dendrimer molecule with drug molecule encapsulated within branches

full generation consists of multiple amines, while the surface of the half generations consists of multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components (Priya et al., 2013).

Methods for characterization of dendritic polymer

The following methods can be used for characterization of dendritic polymer (Achar and Puddephatt, 1994; Miller et al., 1997; Wilken and Adams, 1997; Hummelen, 1997; Kallos et al., 1991; Larre et al., 1998). They are:

Spectroscopy and spectrometric methods

This method is most widely used for characterization of dendritic polymers like.

Nuclear Magnetic Resonance (NMR)

It is a step by step synthesis of dendrimer. It is used for analysis of size, morphology and dynamics of dendrimers for organic dendrimers such as Poly Propylene Imine (PPI).

Ultra Violet Visible Spectroscopy (UV – Visible Spectroscopy)

It is used to monitor the 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

It is used to characterize delocalize π-π stacking interaction between end groups of modified PAMAM.

Fluorescence

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

Raman Spectroscopy

It gave relevant information about the degree of cyclodehydrogenation of polyphenylene dendrimers, and the characterization of PPI and phosphorous dendrimers.

Mass Spectroscopy

Chemical ionization or fast atom bombardment can be used only for the characterization of small dendrimers whose mass is below 300 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 the dendrimer.

Scattering Techniques (Chu and Hsiao, 2001; Prosa et al., 1997; Rietveld and smit, 1999; Topp et al., 1999)

Small angle X-Ray Scattering (SAXS)

It gives information about their average radius of gyration (Rg) in solution. The intensity of the scattering as a functional of angle also provides information on the arrangement of polymer segments, hence on the segment density distribution with in the molecule.

Small angle neutron Scattering (SANS)

It 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 unlabeled end groups.

Laser Light Scattering (LLS)

It is used to determine the hydrodynamic radius of dendrimers. Dynamic LLS is mainly used for the detection of aggregates.

Microscopy Methods (Hafkens et al., 1998; Gensch et al., 1999)

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.

Size Exclusive Chromatography (Zeng et al., 2002)

It allows the separation of molecules according to size.

Electrical Techniques (Francese et al., 2003; Tabakovic et al., 1997; Kukowska-Latallo et al., 1996)

Electron Paramagnetic Resonance (EPR)

It is a quantitative determination of the substitution efficiency on the surface of PAMAM dendrimers.

Electrochemistry

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

Electrophoresis

It is used for the assessment of purify and homogeneity of several type of water-soluble dendrimers.

Rheology and Physical Properties (Mourey et al., 1992; Matos et al., 2000; Dantras et al., 2002; Trahasch et al., 1999)

Intrinsic Viscosity

It is used as analytical probe of the morphological structure of dendrimers.

Differential Scanning Calorimetry

It is used to detect the glass transition temperature which depends on the molecular weight, entangment and chain composition of polymers. information about molecular dynamic processes (α, β).

Miscellaneous (Pavlov et al., 2001; Wooley et al., 1993; Zhuo et al., 1999)

X-Ray Photoelectron Spectroscopy

It is a 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

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

Titrimetry

It is used to determine the number of NH_2 end groups of PAMAM dendrimers.

Other forms of dendrimers

Dendrimers are available in different physical forms for various applications:

Metallo dendrimer

These represent a sub class of dendrimers in which a metal is attached to the dendrimer structure. All metallodendrimers are fully characterized by 1H and 31P NMR Spectroscopy, elemental analysis, and MALDI-TOF mass spectrometry. They have found a wide range of uses that cover Metallo-enzymes, oxidoreductase sensors, medical diagnosis, light harvesting devices, catalysis.

Proteo dendrimer

In these poly anionic hepta (glutamic acids), fluorescent Zinc porphyrintae cores, hydrophilic polyether surfaces, and nonpeptide hydrophobic dendrons are combined, and developed as a new series of synthetic receptors for protein recognition. They have polyanionic patch structures on their surfaces and bear complementary static interactions with a positively charged cytochrome patch, as observed in biological protein-protein recognition systems.

Dendrisomes Supramolecular Assembly of Dendrons

The unique features of dendrimers provide them with the ability to form a variety of supramolecular arrays, some in response to external stimuli. Lipophilic dendrisomes have given their high surface area, without the propensity to aggregate. The cationic branched polylysine dendron with a lipophilic core, a truncated version of a dendrimer that self-assemblies in water forms with and without cholesterol unusual vesicular structures (Dendrisomes) capable of interacting with benzyl penicillin, a model orally labile, negatively charged water-soluble antibiotic. These Dendrisomes have average diameter of around 320nm and zeta potential of +56MV. The Dendrisomes encapsulated penicillin G shows higher entrapment i.e. 6.15% w/w compared to only 1.4% w/w entrapment in case of reverse phase evaporation liposome of 1:1 distearoyl phosphatidylcholine: cholesterol.

Sialodendrimers

These are the products of dendrimers complexed with sialic acid. These are potent inhibitor of haemagglutination of human erythrocytes by influenza viruses. Sialodendrimers bind to haemagglutinin which is crucial for the virus attachment to cell and thus these prevent the attachment of the virus to cells. These can be useful therapeutic agents in the prevention of bacterial and viral infections.

Dendriplexes (Dendron – DNA Complexes)

Cationic dendron and dendrimer lend themselves as non-viral vectors for gene delivery because of their ability to form compact complexes with DNA. A major advantage of dendrimers for in vivo applications is their ability to shield DNA from the action of DNAase found in liquid body

substance. The performance of these vectors differs greatly depending on the physicochemical and colloidal properties of the complexes. Such dendrimer can from complexes with plasmid DNA or antisense oligonucleotides thus protecting the nucleic acids from degradation. Two dendrimer derived products are already in the market as in vitro transfection agents (Shishu and Maheswari, 2009).

Applications of dendrimers

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

Pharmaceutical applications

Dendrimer in Ocular drug delivery

PAMAM dendrimers with radical or hydroxyl radical surface teams, improving residence time and enhance bioavailability of alkaloid with in the eye (Vandamme and Brobeck, 2005; Tolia and Choi, 2008).

Dendrimers in Pulmonary drug delivery

Positively charged PAMAM dendrimers (G2 AND G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin (Bai et al., 2007).

Dendrimers in Transdermal drug delivery

Dendrimers are able to improve drug properties like 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 (Yiyun et al., 2007; Chauhan et al., 2003).

Dendrimers in oral drug delivery

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 (Emanuele et al., 2004; Choi et al., 2005).

Dendrimers in targeted drug delivery

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 (Patri et al., 2002).

Dendrimers for controlled release drug delivery

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 (Asthana et al., 2005).

Dendrimers in gene delivery

Dendrimers are extensively used as non-viral vector for gene delivery. Various polyatomic compound such as PEI, Poly lysine, and cationic have been utilized as non-viral gene carrier (Broeren et al., 2004).

Dendrimer as solubility enhancer

Dendrimers are unimolecular micellar nature, due to have hydrophilic exteriors and hydrophilic interiors and form covalent as well as non-covalent complexes with drug molecules and hydrophobes and enhance its solubilization behavior (Jain and Gupta, 2008).

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 (Najlah and D Emanuele, 2006).

Dendrimers as Nano – Drugs

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 (Boas and Heegaard, 2004).

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 (3nm) cytochrome (4nm) and haemoglobin (5.5nm) are approximately the same size and shape as ammonia-core. PAMAM dendrimers generations 3,4and5 respectively. Generation 2 dendrimer matches the width (2.4nm) of DNA duplexes (from stable complexes with histone clusters to condense and store DNA with in the nucleosome of cells)

and generations 5and6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (5.5nm) of biological cells (Hecht and Frechet, 2001; Jiang and Aida, 1996).

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 example, folate PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron-capture treatment of cancer tumors (Lundquist and Toone, 2002; Zanini and Roy, 1997).

Therapeutic applications

Dendrimers in photodynamic therapy (PDT)

Cancer treatment involving the administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue. For example, the photo sensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes (Svenson and Tomalia, 2012).

Dendrimers for boron neutron capture therapy (BNCT)

The radiation energy generated from the capture reaction of low-energy thermal neutrons by 108 atoms has been used successfully for the selective destruction of tissue. Due to their well-defined structure and multivalency. Dendrimers are very fascinating compounds for use as boron carriers (Barth et al., 1994).

Diagnostic applications

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 (Koten et al., 2000).

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 tumor infarcts kidneys or efferent urinary etc (Schumann et al., 2003; Krause et al., 2000).

Dendrimer 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 (Wiener et al., 1994; Wiener et al., 1997).

Dendritic Catalyst / Enzymes

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 (Kleij et al; Kofoed and Reymond, 2005).

Industrial processes

Dendrimers can encapsulate insoluble materials such as metals and transport them into a solvent with in 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 (Barbara et al., 2001).

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 (Bharali et al., 2009; Kabanov et al., 2002).

- 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).
- 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).
- 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.

Dendrimer based products

The FDA has already approved several dendrimer-based products and some in phase II clinical trials (Singh, 2007; Tang et al., 1996; McCarthy et al., 2005). 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.
- ✓ Vivage for preventing HIV.

PPI dendrimers

Poly (propylene imine) dendrimers have also been called Astramol dendrimers, or simply have been abbreviated as PPI Dendrimers or as DAB-Am-x dendrimers. DAB stands for diamino butane core, and x=4,8,16,32 or64 for the number of primary amine end groups associated with the generations 1,2,3,4 or 5 respectively. Below the molecular structure of the fourth and fifth generation (G4 and G5) amine terminated PPI-Dendrimer (or DAB-Am-32 and DAB-Am-64).

Synthesis of PPI dendrimers

Synthesis of Divergent Method

The divergent method is used for the synthesis of PPI Dendrimers. A new dendrimers generation arises with each branching units. The repetitive synthetic sequence, consisting of both the construction step, in which coupling of a branching unit to two further units (1-2 branching) takes place, as well as the activation step increasingly yields higher generations and permits the dendrimers to grow from the inside outwards. An advantage, of the divergent method which was the first to be developed, is the attainable higher molecular nano scaffold architecture as well as the possibility of automation of the repetitive steps.

Due to the increasing number of functional end groups because of excess number of reactants, none of them can react properly with dendritic units and structural defect will happen. Because of the similarity of the properties of perfect and imperfect dendrimers, separation and purification of final products is very difficult and sometimes impassible. These problems are disadvantages of divergent synthetic method.

Design of the synthesis of PPI dendrimer

The PPI Dendrimer consists of a repetition of a double Michael addition of acrylonitrile to primary amines, followed by the hydrogenation of terminal nitrile groups.

Divergent synthesis methodology pf PPI dendrimers is based on the theory developed by Vogtle et al in 1978. Acrylonitrile is reacted with a primary mono or oligo diamine and then reduced in present of CO (II) acetate and sodium borohydride.

Following repetitive reaction cycles permit repeated addition of acrylonitrile followed by reduction until the limiting generation reached. In 1993 almost at the same time, researchers accomplished the preparative synthesis of higher generations of mono-disperse PPI dendrimers.

Investigation of nano –scale of PPI dendrimer Dendrimers are nano – scale symmetric molecules homogeneous and monodisperse structure consisting of tree – like arms or branches. At a molecular nano – scale level, dendrimers like branching polysaccharides, have an elegant solubility to a cell because of the presence of many chain end linked to functional end groups in periphery of dendrimers which allows the rapid release of large number of glucose monomers when needed (Figure 6).

Dendrimers have a small degree of polydispersity because

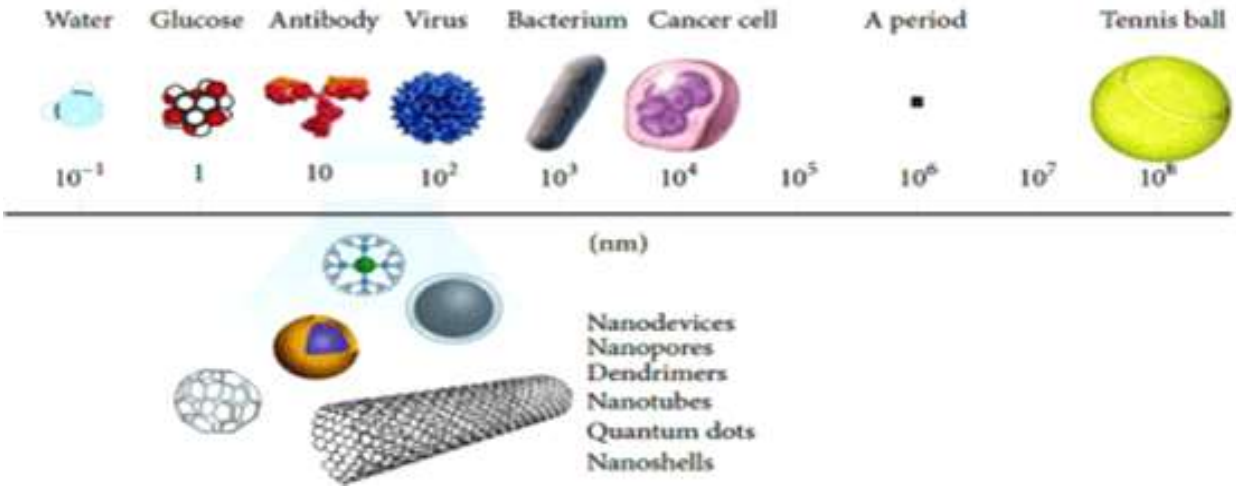

Figure 6. Nano – scale of dendrimers in compare with other molecules

Table 3. PPI parameters with the number of generations

S. No.	Generation	End group (number)	Diameter (nm)	Molar Mass (g)
1	1	4	0.44	317
2	2	8	0.69	773
3	3	16	0.93	1687
4	4	32	1.16	3514
5	5	64	1.39	7168

unlike classical polymerization that is random in nature and produces, molecules of varied sizes but the size of dendrimers are often carefully controlled during synthesis. Under ideal conditions, preparation of dendrimers is monodispersed which is to say they have one molecular weight instead of the mixture of many molecules with different molecular weight. Electron micrographic studies showed the dendrimer with carboxylate groups of generation, to be highly mono-dispersed with a diameter in nanometer. PPI dendrimer is also nano – scale which in table 3, defined diameter of any generations of it.

Conclusion

The main conclusion of this review is the dendrimer structure, property, size and shape, functionality, branching. The various applications of dendrimers like therapeutic, diagnostic, catalyst and drug delivery. Bioavailability, Permeability, poor solubility, toxicity and biocompatibility can be overcome by use it. Recent success in optimizing and simplifying the synthesis of dendrimers provide a large variety of structures with decreased cost of their production. Dendrimers can be synthesized by mainly two methods, they are: Convergent method and Divergent method. Dendrimers are also used to improve the solubility of different drugs. The new dendrimer technologies will emerge and a growing number of commercialized dendrimer-based drug delivery systems are expected to emerge in the future.

Conflict of interest: None

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