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Dendrimers- a novel drug delivery system

Patel Shiv Narayan*, Sethi Pooja, Ansari Khushboo, Tiwari Diwakar, Sharma Ankit and Singhai A.K.

Lakshmi Narain College of Pharmacy, Bhopal, (M.P.) -India

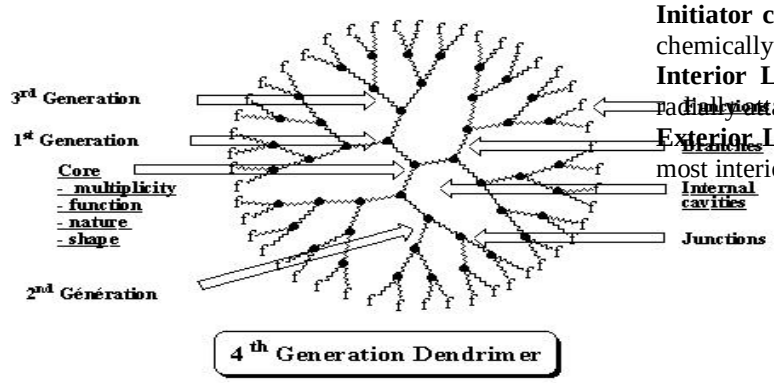
Abstract

Dendrimers are the polymeric materials for targeted delivery of drug molecule. These are the highly branched nanoscopic structure for the potential delivery of bioactive. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached i.e. conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. In addition to supplying a multivalent backbone for drug attachment, dendrimers also provide access to various new polymer architectures that are potentially relevant to drug delivery applications. Through this review we are mainly focusing on the various properties and applications of dendrimer in pharmaceutical sciences.

Keywords: Dendrimers, Drug delivery, Polymers

Introduction

Dendrimer are defined as a high molecular weight, highly branched nanoscopic, polymeric 3-d structure for potential delivery of bio actives. First discovered in the early 1980's by Donald Tomalia and co-workers, these hyper branched molecules were called dendrimer. The term originates from 'dendron' meaning a tree in Greek. At the same time, Newkome's group independently reported synthesis of similar macromolecules. They called them arborols from the Latin word 'arbor' also meaning a tree. The term cascade molecule is also used, but 'dendrimer' is the best established one. Dendrimer (G) n undergoes chemical bridging to form starburst polymer Gn. As the chemical reaction occur between nucleophillic and electrophillic surface of dendrimer, enhancement of dimension to about 100 nm occur, as a result nanoscopic supramolecular compound formed called as starburst polymer which was observed by electron microscopy. General structure of dendrimer is shown below.[1-3]



Initiator core- Initiator core must have atleast three chemically reactive arms.

Interior Layer- Interior layer is a repeating units radially attach to the initiator core.

Exterior Layer- Exterior layer attached to the outer most interior layer.

*** Corresponding Author:**
E-mail: shiv_narayan2929@yahoo.com

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Various components of dendrimers[3-10]

1. Generations- From the centre of dendrimer i.e. core to the periphery, branching increases and a homostructural layer between a focal point or branching point is formed, number of focal point from centre to periphery is called as generation number.

Eg- G 0 generation – initiator core has no focal points i.e. hydrogen substitutes

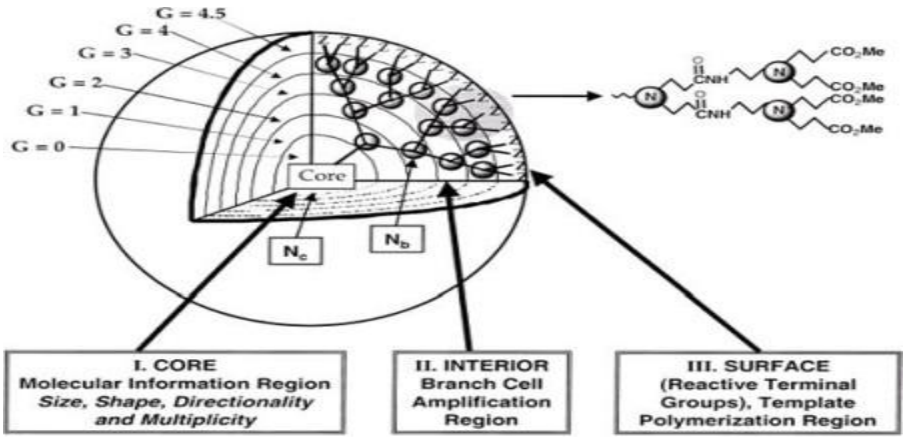
G-5 generation- polypropylene amine (G-5 PPI)

Intermediate form during the dendrimer synthesis has a half generation e.g. carboxylic acid terminated PAMAM dendrimers.

2. Shell (Generation Space) - Shell is a homostructural spaces between a focal point. Outer shell is a space between a focal point and surface while inner shell is a interior of dendrimer.

3. Pincer- Outer most shell has a varying number of pincer created by last focal point before reaching to the surface. E.g. PPI and PAMAM dendrimer has number of pincer half the number of surface groups.

4. End Group- End groups are the surface or terminal group of dendrimer e.g. amino terminated dendrimer has a amine end group.



Molecular modelling of dendrimers

Starburst effect: Minimum density at the centre of dendrimer predicts that the ideal dendritic growth will not occur until the certain generation is reached and at which point the steric congestion will prevent the further growth.

Computer assisted molecular modelling: The shape of starburst dendrimer is open structure and as the size increases it gets closed with well developed internal hollows and dense surface.

Back folding of chains: Radius of gyration depend upon the polarity of solvent and increases with the increase in generation. High ionic strength causes the back folding of chains while low ionic strength causes molecule to stretch to form dense shell.

Type of dendrimers[9-16]

Pamam dendrimer: Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10 (a molecular weight of over 9,30,000 g/mol) have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, usually as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the starlike pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

Metallo dendrimer: Dendrimer is attached to metal ion by complexation either interiorly or at the periphery.

Liquid crystalline dendrimer: Liquid crystalline dendrimer consist of mesogenic momomer units.

Pamamos dendrimer: Radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

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PPI dendrimer: PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle. These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine), which closely resembles the PPI abbreviation. In addition, these dendrimers are also sometimes denoted "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

Tecto dendrimer: These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

Multilingual dendrimers: In these dendrimers, the surface contains multiple copies of a particular functional group.

Chiral dendrimers: The chirality in these dendrimers are based upon the construction of a constitutionally different but chemically similar branches to chiral core.

Hybrid dendrimers: Linear Polymers- These are hybrids (block or graft polymers) of dendritic and linear polymers.

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

Micellar dendrimers: These are unimolecular micelles of water soluble hyper branched polyphenylenes.

Multiple antigen peptide dendrimers: It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, e.g. vaccine and diagnostic research.

Frechet-type dendrimers: It is a more recent type of dendrimer developed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers usually 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.

Table 1: Properties of dendrimer and linear polymers

S/ No.	Property	Dendrimers	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	Crystallanity	Non-crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7	Aqueous solubility	High	Low
8	Nonpolar solubility	High	Low
9	Viscosity	Non linear relationship with molecular weight	Linear relation with molecular weight
10	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydisperse

Synthesis of dendrimer

Divergent method: In the divergent methods, dendrimer grows outwards from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers.

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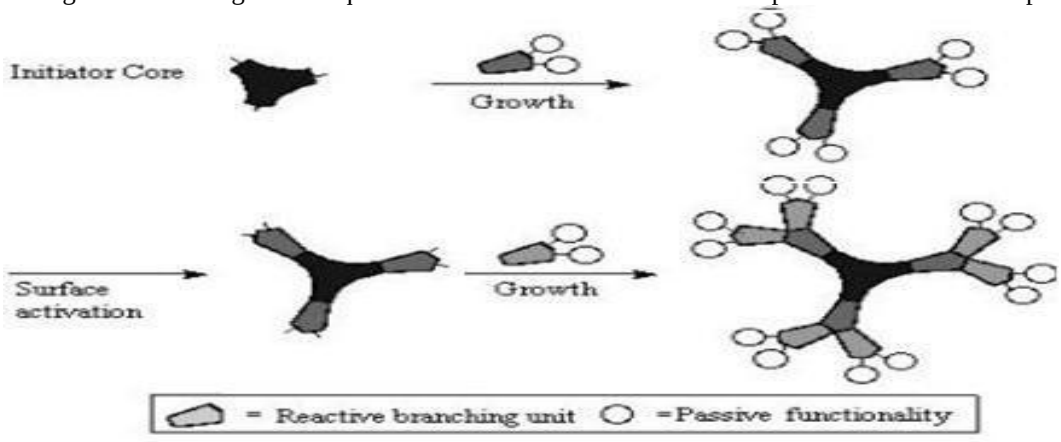
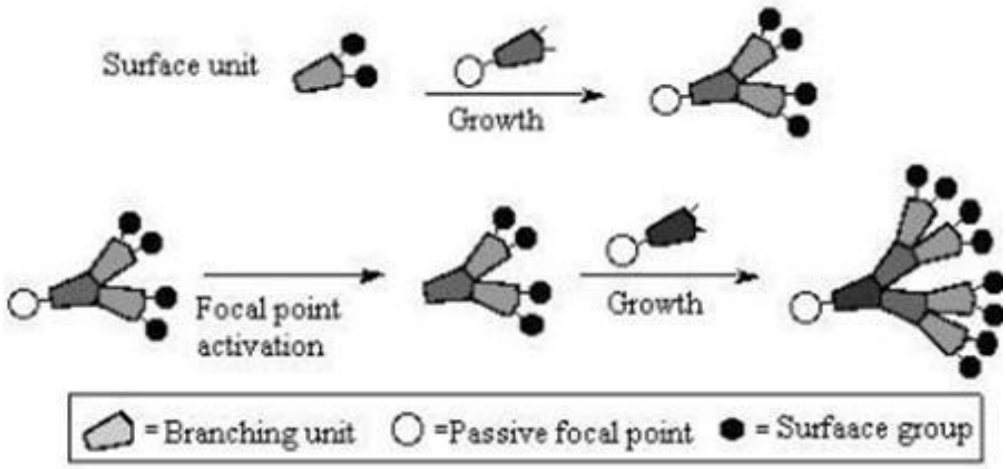
The process is repeated for several generations and a dendrimer is built layer after layer. The divergent approach is successful for the production of large quantities of dendrimers. Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. It causes some difficulties in the purification of the final product.



Convergent method: The convergent methods were developed as a response to the weaknesses of the divergent synthesis. In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule. The convergent growth method has several advantages. It is relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule.



Double exponential and mixed growth: The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' growth. A schematic representation of double exponential and mixed growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB_2 monomer with orthogonal protecting groups for the A and B functionalities. This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material. These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again.

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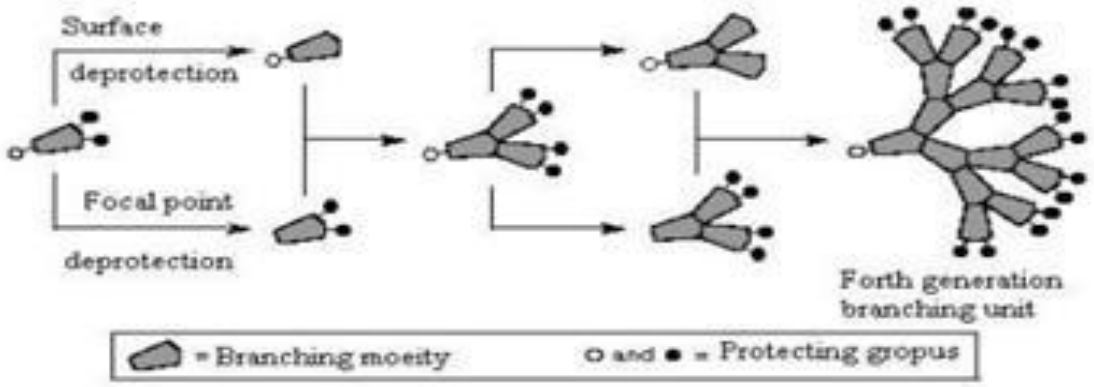
The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. The double exponential methodology provides a means whereby a dendritic fragment can be extended in either the convergent or the divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings.



Evaluations of dendrimers[15-19]

Molecular weight homogenicity, interior or end group dimension: Mass spectroscopy, chemical ionization, fast atom bombardment, size exclusion chromatography, electron microscopy, infra red spectroscopy, nuclear magnetic resonance, titrimetry.

Sensitivity, perfection of dendrimer: MALDI (matrix assisted laser desorption ionization), ESI (electro spray ionization).

Radius of gyration of dendrimer: Scattering techniques

Image of individual dendrimer molecule: Transmission electron microscopy, atomic force microscopy.

Invitro evaluation: Monolayer vero cell cell placed in a 6 well plates which is incubated at 37 degree Celsius. Different concentration of dendrimers ranging from 0.01 to 30 ug/ml and 100 HSV-2 strains –G added to cell and incubate for 1 hour. After inoculation, cell was washed with phosphate buffer saline and then overlaid with 0.5% methyl cellulose for plague assay. After 2 days monolayer fixed with 10% formaline and then stained with 0.5% crystal violet and EC 50 value were calculated.

Application of dendrimers[15-22]

Dendrimer as a solubility enhancer: One molecule of dendrimer solubilizes 0.45 molecule of pyrene. If Nacl is added, due to the quenching of the water molecule from the interior of dendrimer, it is able to solubilize 1.9 molecule of pyrene. The solubility efficiency of dendrimer is comparable with sodium lauryl sulpahte.

Non viral gene delivery- Gene expression system encoding desired gene an different concentration of dendrimer, there is a electrostatic interaction between terminal amine group of dendrimer and phosphate group of DNA molecule and thus efficient in non viral gene delivery.

Dendrimer based drug delivery: Dendrimer have the3-d highly branched structure, thus availability of many functional groups at the surface. The drug may bind to the interior of dendrimer and thus encapsulating the drug within the dendritic structure or the drug may bind to the surface via functional group i.e. covalent bonding. Hence providing targeted as well as controlled delivery of drugs.

Dendrimers as nano-drugs: 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). In earlier studies, it was found that PAMAM dendrimers covalently modified with naphthyl sulfonate residues on the surface, also exhibited antiviral activity against HIV.

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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. 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. 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. Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications.

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

Dendrimers in gene transfection: Dendrimers can act as vectors**,** in gene therapy. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of 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. A transfection reagent called SuperFectTM consisting of activated dendrimers is commercially available. Activated dendrimers can carry a larger amount of genetic material than viruses. SuperFect–DNA complexes are characterized by high stability and provide more efficient transport of DNA into the nucleus than liposomes. The high transfection efficiency of dendrimers may not only be due to their well-defined shape but may also be caused by the low pK of the amines (3.9 and 6.9). The low p*K* permit the dendrimer to buffer the pH change in the endosomal Compartment . PAMAM dendrimers functionalized with cyclodextrin showed luciferase gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and cyclodextrin . It should be noted that 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 than intact high-generation symmetrical Dendrimers .

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