

Available online on 15.09.2014 at <http://jddtonline.info>**Journal of Drug Delivery and Therapeutics**

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## REVIEW ARTICLE

**DENDRIMERS: A NOVEL CARRIER SYSTEM FOR DRUG DELIVERY**Dwivedi Devendra Kumar\*, Singh Arun Kumar<sup>1</sup>

Devsthali Vidyapeeth College of Pharmacy, Lalpur, Rudrapur (U.K.), India

\*Corresponding Author's Email: [devendra.bpharm@gmail.com](mailto:devendra.bpharm@gmail.com)**ABSTRACT**

Dendrimers are a novel class of structurally controlled macromolecules which have the structure like a tree or star shape, with a central core, interior branches and terminal groups decorate the surface and from the cavity inside the core. Cavities inside the core and the interior branches help to carry hydrophobic and hydrophilic drugs. The terminal groups on the surface can also be adapted for drug targeting purposes. Dendrimers are generally prepared using either a divergent or a convergent method. Dendrimers have well defined size, shape, molecular weight and monodispersity. These unique properties make them a suitable carrier in drug delivery application. It has branched mono-dispersed polymer having 5-50 nanometers in diameter with unique structural and topological features. Dendrimers are easily characterized by spectroscopic techniques, microscopy as SEM, TEM, size exclusion chromatography, electrical techniques, and rheology, physical properties. Dendrimers are compatible with DNA, heparin and polyanions make them more versatile novel drug delivery. These artificial macromolecules may be manipulated nano size range, similar to proteins. The drug can be easily encapsulated into the inner core of the dendrimers or chemically attached that is 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. Recent investigations suggest that dendrimers can be used as a promising nanocarriers for drug delivery system to enhance the absorption of drug and biocompatibility. This review highlights the various aspects of dendrimers including properties, and their versatile application in drug delivery system.

**Keywords:** Dendrimers, biocompatibility, bioavailability, novel drug delivery.

**1 INTRODUCTION**

Dendrimers are a novel class of structurally controlled macromolecules which have the structure like a tree or star shape, with a central core, interior branches and terminal groups decorate the surface and from the cavity inside the core. Dendrimers have well defined size, shape, molecular weight and monodispersity and reactivity are determined by generation (shells) and chemical composition of the core, interior branching, and surface functionalities. It has branched mono-dispersed polymer having 5-50 nanometers in diameter with unique structural and topological features, by these properties, now a day it has considerable interest from both scientists and researchers<sup>1</sup>. Dendrimers are just in between molecular chemistry and polymer chemistry. Dendrimer oligonucleotide are representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers. He synthesized the first "cascade molecules" later it was called dendrimer<sup>2</sup>. The word "dendrimer" originated from two words, the Greek word dendron, meaning tree, and meros, meaning part. Newkome's and coworkers independently reported synthesis of similar macromolecules. They called them arborols from the Latin word 'arbor' also meaning a tree<sup>3</sup>. Dendritic polymers are nanostructures that are suitable for drug solubilization applications, delivery of DNA and oligonucleotide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug

delivery system. Dendrimers are core-shell nanostructures with precise architecture and low polydispersity, which are synthesized in a layer-by-layer fashion (expressed in 'generations') around a core unit, resulting in high level of control over size, branching points and surface functionality. The ability to tailor dendrimer properties to therapeutic needs makes them ideal carriers for small molecule drugs and biomolecules. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular<sup>4</sup>.

**2 STRUCTURE OF DENDRIMER**

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions for the production of a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex<sup>5</sup>. The performance of these dendrimers are dependent upon its size, generation and surface functional groups with increase in dendrimer generation the dendrimer, the dendrimer increase linearly while the number of surface group increases exponentially<sup>6</sup>.

## The Dendritic Structure

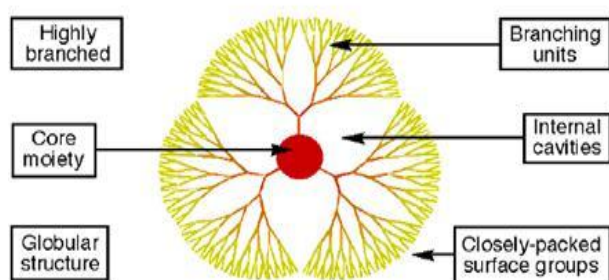


Figure 1: The Dendrimer Structure

Typical dendrimers are globular nanoscale macromolecules with a particular architecture constituted of three distinct regions as shown in (Figure.1).

- An initiator core.
- Interior layers (generations) composed of repeating units, radially attached to the interior core.
- Exterior (terminal functionality) attached to the outermost interior generations.

### 3 TYPES OF DENDRIMERS<sup>7,8</sup>

- PAMAM Dendrimer monodisperse
- PPI Dendrimer polymers
- PAMAMOS Dendrimers
- Chiral Dendrimer
- Hybrid Dendrimer
- Amphiphilic Dendrimer
- Multilingual Dendrimer
- Tecto Dendrimer
- Frechet-Type Dendrimer
- Peptide Dendrimer

#### 3.1 PAMAM Dendrimers:

Synthesis of Poly (amidoamine) dendrimers (PAMAM) by the divergent method starting from ethylenediamine or ammonia 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. Trademark name is Starburst dendrimers. It is applied as a subclass of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions<sup>7</sup>.

#### 3.2 PPI /POPAM Dendrimers:

PPI means Poly (Propylene Frechet-Type Dendrimers: These are based on Imine)/Poly (Propylene Amine. 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.

#### 3.3 PAMAMOS Dendrimers:

Poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles. It consists of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. This is useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

#### 3.4 Chiral Dendrimer:

Chiral Dendrimers are commercial dendrimers. These are inverted unimolecular based upon the construction of constitutionally different micelles that contain exterior hydrophobic organosilicon but chemically similar branches to chiral core.

#### 3.5 Hybrid Dendrimer:

Hybrid dendrimers are combination of dendritic and linear polymers in hybrid block or graft copolymer forms<sup>8</sup>.

#### 3.6 Amphiphilic Dendrimer:

These are formed by two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

#### 3.7 Multilingual Dendrimer:

The surface of these dendrimers contains multiple copies of a particular functional group.

#### 3.8 Tecto Dendrimer:

These are core dendrimers which is surrounded by other dendrimers, each one of which perform a specific varied function ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

#### 3.9 Frechet-Type Dendrimer:

It is a more new type of dendrimer formed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. In the surface of these dendrimers carboxylic acid groups are attached. This is 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.

#### 3.10 Peptide Dendrimer:

Peptide dendrimers are those which contain amino acid as branching or interior unit. These are used for diagnostic purpose and vaccine delivery<sup>9</sup>.

### 4 SYNTHESIS OF DENDRIMERS<sup>8,10</sup>

Dendrimers are generally prepared using either a divergent or a convergent method. There is a fundamental difference between these two construction methods.

#### 4.1 Divergent Method

In this method, dendrimer develops from a multifunctional core molecule. The reaction of core molecule with monomer molecules which contains one reactive and two dormant groups formed the first generation dendrimer. Then this new periphery of first generation dendrimer is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built after several layer of reaction. Divergent approach is more useful 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. (Fig.2)

#### 4.2 Convergent Method

The convergent methods were developed as to minimize the problems of the divergent synthesis. In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups (beginning from the leaves of the molecular tree) and progressing inwards. When the dendrons are developed, they are attached to a multifunctional core molecule (Fig. 2). The convergent growth method has several advantages. It is more suitable to purify the desired product and the occurrence of defects in the final structure is minimised. By this method introduction of subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule is possible. This approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule.

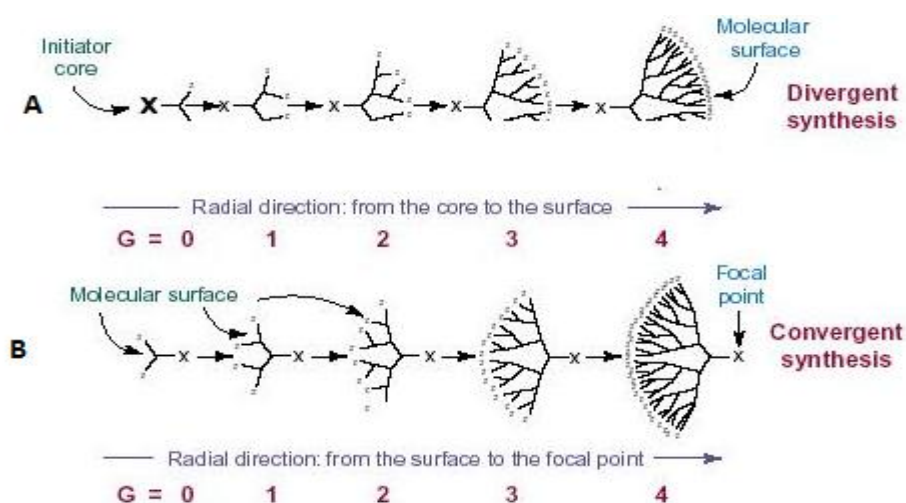


Figure 2: Synthetic methods for constructing dendritic macromolecules (Dendrons): (A) the divergent method (B) the convergent method.

### 5 CHARACTERIZATION OF DENDRIMERS<sup>11, 12, 14</sup>

#### 5.1 Spectroscopy technique:

##### 5.1.1 Nuclear Magnetic Resonance (NMR):

Nuclear Magnetic Resonance is most widely used for characterizing of dendrimers. NMR mainly used for analyzing step by step synthesis of dendrimer, to probe the size, morphology, dynamic of dendrimers, for organic dendrimers such as PPI, polyphenylester.

##### 5.1.2 UV-Visible Spectroscopy:

UV-Visible spectroscopy can be used to monitor the synthesis of dendrimers, as shown for organoplatinum dendrimers in which a growth and decay of the metal to ligand charge transfer band is observed. The intensity of the absorption band is essentially proportional to the number of chromophoric units, and can be a test for the purity of PPI dendrimers having azobenzene as end groups, for phosphorus dendrimers having azobenzenes within the branches, or double-layered carbosilane dendrimers.

##### 5.1.3 Infra-red (IR) and Raman Spectroscopy:

Infra-red spectroscopy is mainly used for the routine analysis of the chemical transformations occurring at the surface of dendrimers, such as the disappearance of nitrile groups in the synthesis of PPI dendrimers, the occurrence of hydrogen bonding in PPI glycine functionalized dendrimers, or the disappearance of the aldehydes during the synthesis of PMMH dendrimers.

##### 5.1.4 Fluorescence:

The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers, such as unreacted CO<sub>2</sub>H groups in ARB dendrimer, but its main use is to characterize the structure of dendrimers having photochemical probes covalently linked to one particular section.

##### 5.1.5 X-ray diffraction:

This technique should allow precise determination of the chemical composition, size and shape of dendrimers.

### 5.1.6 Mass spectrometry<sup>13</sup>:

Classical mass spectrometry techniques such as chemical ionization or fast atom bombardment (FAB) can be used only for the characterization of small dendrimers, whose mass is below 3000 D. Electro-Spray Ionisation (ESI) can be used for dendrimers able to form stable multicharged species. It has been applied to PPI dendrimers, and to PAMAM dendrimers up to generation 10.

### 5.2 Microscopy:

Transmission electron microscopy and Scanning electron microscopy are mainly used for imaging of dendrimers. Visualizing single molecules by optical microscopy has been successfully carried out for dendrimers having a fluorescent core. Confocal microscopy allowed observing the fluorescence of a third generation PBzE dendrimer having a dihydropyrrolo pyrroledione as a core, and of polyphenylene dendrimers having peryleneimide as end groups.

### 5.3 Size exclusion chromatography (SEC):

Size Exclusion (or Gel Permeation) Chromatography allows the separation of molecules according to size. A detector such as a differential refractive index or a LLS detector is connected to the SEC apparatus for the determination of the polydispersity, which is generally very close to unity. Most types of dendrimers were characterized by SEC, even self-assembled dendrimers.

### 5.4 Electrical techniques:

**5.4.1 Electron Paramagnetic Resonance:** Quantitative determination of the substitution efficiency on the surface of PAMAM dendrimers.

### 5.4.2 Electrochemistry:

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

### 5.4.3 Electrophoresis:

Used for the assessment of purity and homogeneity of several types of water soluble dendrimers.

### 5.5 Rheology, physical properties:

**5.5.1 Intrinsic viscosity:** Rheology, and particularly dilute solution viscosimetry studies, can be used as analytical probe of the morphological structure of dendrimers.

### 5.5.2 Differential Scanning Calorimetry (DSC):

The DSC technique is generally used to detect the glass transition temperature (T<sub>g</sub>), which depends on the molecular weight, entanglement and chain-end composition of polymers. The T<sub>g</sub> is affected by the end group substitutions, and the molecular mass for PBzE dendrimers.

**5.5.3 Dielectric spectroscopy (DS):** Dielectric spectroscopy gives information about molecular dynamic processes in polymers (α-, β-, γ-, and δ-relaxation).

## 6 APPLICATIONS IN DRUG DELIVERY

The development of an efficient drug delivery system is very important to improve the pharmacokinetic and pharmacodynamic activity of drug molecules.

Dendrimers as carrier have proceeded from as new alternatives and efficient tools for delivery of drug molecules. As compared to linear polymeric carriers, the multivalent functionalities of dendrimers can be linked to drug molecules or ligands in a well-defined manner and can be used to increase the binding efficiency and affinity of therapeutic molecules to receptors via synergistic interaction<sup>15</sup>.

### 6.1 Oral drug delivery:

Oral drug delivery systems are very important and convenient and common illnesses are treated via oral route of medication. Dendrimers are biodegradable, and capable to hold the drug with good. By combining the ideas of drug carriers and degradability, research has recently focused on controlled degradation of dendrimers and release of compounds via oral route. Encapsulation and conjugation of drug with dendrimers have shown immense employment for delivery of hydrophobic and labile drugs. Transport of dendrimers throughout epithelial part of gastrointestinal tract depends upon its characteristics. Anticancer and antihypertensive drugs are most promising candidate for oral route using dendrimer as carrier.

Dendrimers with diameters in the range of 2.5 to 6 nm seemed to offer the ideal progression to smaller and smaller systems. Problem of flocculation and aggregation of the system in vivo, oral uptakes of dendrimers are not better as accepted. Using polyoxyethylene glycol chains or ionic groups can reduce this problem, but oral uptake is then hindered by the hydrophilic nature of the surface dendrimers. Dendrimer-drug size, molecular weight, surface charge, incubation time and concentration of active molecule impart different characteristics for oral delivery of dendrimers<sup>16</sup>.

### 6.2 Ocular drug delivery:

The topical application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor. These results mainly due to drainage of the excess fluid via nasolacrimal duct and elimination of the solution by tear turnover. Dendrimers provide a choice formulation for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability<sup>17</sup>.

### 6.3 Transdermal drug delivery:

Now a day's dendrimers have found applications in transdermal drug delivery systems. Dendrimers designed to be highly water-soluble and biocompatible have been shown to be able to improve drug properties such as solubility and systemic circulation time via transdermal formulations and to deliver drugs efficiently. The viscosity imparting property of a dendrimer solution allows for ease of handling of highly concentrated dendrimer formulations for these applications. Dendrimers have been shown to be useful as transdermal drug delivery systems for nonsteroidal anti-inflammatory

drugs (NSAIDs), antiviral, antimicrobial, anticancer, or antihypertensive drugs. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAIDs: ketoprofen and diflunisal<sup>18</sup>.

#### 6.4 Targeted gene delivery:

Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Currently liposomes and genetically engineered viruses have been mainly used for this. PAMAM dendrimers have also been tested as genetic material carriers. Cationic dendrimers (Polypropylenimine (PPI) dendrimer) deliver genetic materials into cells by forming complexes with negatively charged genetic materials through electrostatic interaction. Cationic dendrimers lend themselves as non-viral vectors for gene delivery because of their ability to form compact complexes with DNA. Another potential application could be the use of dendrimers coated with sialic acid for the influenza virus to attach to the cell surface. In addition, dendrimers are non-immunogenic and are thus uniquely suited as carrier structures for drugs or bioactive molecules without degradation in immune system. Although the application of dendrimers in the field of drug and gene delivery is in its infancy compared to liposomes and other nanomaterials. Dendrimers are already making an impact with the first therapeutic product based on dendrimer technology, Vivagel™ topical micobicide, currently undergoing phase-II trial<sup>17, 18</sup>.

#### 6.5 Dendrimers as Solubility Enhancer:

Dendrimers are unimolecular micellar in nature because these have both hydrophobic and hydrophilic layer. Hydrophilic layer forms the core and hydrophobic layer forms the outer surface. Dendrimers do not have a critical micelle concentration. Due to these properties dendrimers enhance the solubility of poorly soluble drug by forming covalent, non-covalent complexes with drug molecules and hydrophobes.

#### 6.6 Current and Potential Applications of Dendrimers<sup>19</sup>:

- Delivery of Nucleic acids encapsulated drugs and covalently linked drugs.
- Modification of cell-cell interactions and gene expression (e.g.: alteration of transcription factors binding to DNA).
- 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.
- New carrier system for drug delivery (gels, self-associating systems).
- Vaccines against bacteria, viruses and parasites.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.

#### CONCLUSIONS

Due to their unique structure dendrimers have improved physical and chemical properties. These have well defined size, shape, molecular weight, monodispersity and are unimolecular micellar in nature. These properties make the dendrimers a smart choice for drug delivery application and enhance the solubility of poorly soluble drug. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

#### ACKNOWLEDGEMENTS

The authors wish to thank Dr. D.K. Sharma (Principal), A.K. Singh (HOD) Devsthal Vidyapeeth College of Pharmacy, Lalpur, Rudrapur, for their kind support and encouragement me to carry out this work.

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