JGTPS, 2015, Vol. 6(3): 2860 - 2866

ISSN- 2230-7346

Journal of Global Trends in Pharmaceutical Sciences

Journal home page: www.jgtps.com

DENDRIMERS – STRUCTURE, SYNTHESIS, ENCAPSULATION, CHARACTERIZATION AND APPLICATIONS

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ABSTRACT

Dendrimers are a novel class of polymeric materials. Dendrimers are hyper branched macromolecules characterized by its surface functionality and versatility. Structural perfection make Dendrimers a potential item in the fields of nanotechnology, medicinal and pharmaceutical chemistry etc. Dendrimers also possess applications in industrial and biomedical areas. Several properties of Dendrimers are dominated by the surface functional groups. It is possible to incorporate a hydrophobic drug within the water-soluble dendrimer. Thus encapsulation property offers stability to the poorly soluble drugs. Volume of dendrimer increases when it has a positive charge. This property of Dendrimers can be utilized in treating various diseases inside the patient's body. Dendrimers can be synthesized using divergent, convergent and double-exponential methods. Through this review, we will be mainly focusing on the structure, components, synthesis methods and applications of Dendrimers.

Key words: Dendrimers, Encapsulation, PAMAM Dendrimers, Drug Delivery

INTRODUCTION:

Novel drug delivery systems have created a revolution in the field of medical sciences with its novel approaches towards diagnosing and treating several diseases. Novel dosage forms include niosomes, liposomes, proniosomes, ethosomes, aquasomes, Dendrimers etc. Of them, Dendrimers found to be the unique systems with their improved physical and chemical properties and three dimensional architecture [1]. A dendrimer is a macromolecule characterized by highly branched 3D structure, uniform size, water solubility, multiagency, well defined molecular weight and available internal cavities, makes them attractive carriers and also find applications in effective drug delivery.

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Dendrimer was first introduced by in 1978 by Fritz Vogtle and coworkers in 1978 by synthesizing the first "cascade molecules". Later in the year 1985, Donald A. Tomalia, synthesized the first family of Dendrimers. The word "dendrimer" originated from two words, the Greek word *dendron*, meaning tree, and *meros*, meaning part. Dendrimers are in between the molecular and polymer chemistry. Their step by step controlled synthesis makes them to retain the characteristics of molecular chemistry and their repetitious branching makes them the members of polymer chemistry. Dendrimers are synthetic nano-materials with diameter range 2-10 nm size. Their unique architectural design, repetitious branching, globular structure,
multivalency, mono-dispersity makes them suitable agents in the fields like gene therapy, chemotherapy etc [2,3].

STRUCTURE OF DENDRIMERS:

Generally Dendrimers are constructed from a starting atom, such as nitrogen. By a series of chemical reactions, other elements like carbon get attached to the nitrogen giving out a spherical branching structure. As this process repeats, successive layers are added, and the sphere can be

expanded to the size required. Dendrimers possess 3 distinguished architectural components, namely:

- An initiator core
- Interior layers (generations) composed of repeating units that are radically attached to the interior core.
- Exterior (terminal functionality) attached to the outermost interior generations [4].

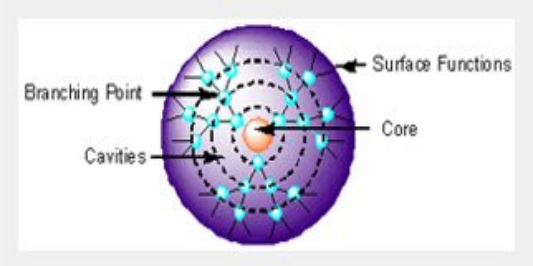

Fig 1: Structure of dendrimer

The core of the dendrimer is may be a single atom or group of atoms. To this core several layers get added radially leading to the formation of dendritic generations and terminal groups are located to the exterior of the dendrimer. Dendrimers of lower generations (0, 1 and 2) possess highly asymmetric shape when compared to Dendrimers of higher generations. The layers that grow from the core molecules become larger and more branched enough to build a characteristic globular size of the dendrimer [5].

Components of Dendrimers:

There are four main components of the dendritic structure.

a. **Generation:**

It is the hyper branching or successive layers formed when going from the centre towards the periphery of the dendrimer. The number of focal points between the core molecule and dendrimer surface is the generation number. A dendrimer with five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer.

b. **Shell:**

The dendrimer shell is the homo-structural spatial segment between the focal points, referred as the "generation space". The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred to as the dendrimer interior.

c. **Pincer:**

The outer shell of dendrimer consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface.

E.g.: In PPI and PAMAM Dendrimers the number of pincers is half the number of surface groups.

d. **End-group:**

End groups are also referred to as the "terminal groups" or the "surface groups" of the dendrimer.

E.g.: Dendrimers with amine end-groups are referred as amino-terminated Dendrimers [6,7].

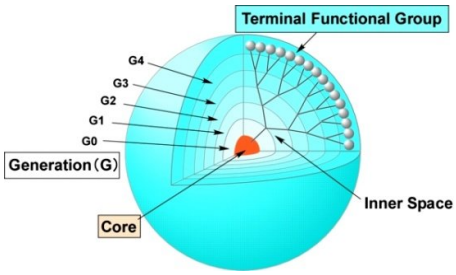

Fig. 2 Components of Dendrimers

TYPES OF DENDRIMERS:

PAMAM Dendrimer: Poly (amidoamine) Dendrimers

They are synthesized from ammonia or ethylenediemine as the starting core material by the divergent method. Products up to generation 10^9 have been synthesized and their respective molecular weight is around 9, 30,000g/mol. PAMAM Dendrimers are commercially available as methanol solutions.

PAMAMOS Dendrimer: Radially layered poly (amidoamine- organosilicon) Dendrimers (PAMAMOS) These are the inverted unimolecular micelles containing both hydrophilic- nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors.

PPI Dendrimer: PPI-Dendrimers stand for "Poly (Propylene Imine)".

These Dendrimers are the poly-alkyl amines with primary amines as end groups. The interior of the dendrimer consists of several tertiary tris-poly propylene amines. PPI Dendrimers are commercially available up to G5. These Dendrimers have vast applications in the fields of material science and biology [8].

Tecto Dendrimer:

In this type, there is a core dendrimer surrounded by various other Dendrimers, designed to perform various functions like diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

Multilingual Dendrimers:

In this type of Dendrimers, the surface possesses multiple copies of a particular functional group.

Chiral Dendrimers:

Chiral dendrimer is an optically active dendrimer. Its construction is different constitutionally but possesses chemically similar branches to its chiral core.

Hybrid Dendrimers Linear Polymers:

These Dendrimers are the hybrids of both dendritic and linear polymers.

Amphiphilic Dendrimers:

These Dendrimers are built from two segregated sites of a chain end. One half of the chain is electron donating and the other half is electron withdrawing [9].

Micellar Dendrimers:

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

Frechet-Type Dendrimers:

It is a more recent type dendrimer being developed by Hawker and Fréchet. They have carboxylic acid groups as surface groups that serves as a good anchoring point for further surface functionalisation. Due to the presence of polar surface groups, the solubility of this hydrophobic dendrimer type is increased in polar solvents and aqueous media [10].

Table 1: Properties of dendrimers: [11]

S.no	Property	Dendrimers
1.	Structure	Compact, globular
2.	Synthesis	Careful, stepwise
3.	Structural Control	Very high
4.	Architecture	Regular
5.	Shape	Spherical
6.	Viscosity	Non-linear relationship with molecular weight
7.	Aqueous solubility	High
8.	Non-polar solubility	High
9.	Reactivity	High
10.	Poly-dispersity	Mono-disperse
11.	Crystallinity	Non-crystalline amorphous materials with low glass temperature.
12.	Compressibility	Low

Synthesis of dendrimers:

Dendrimers can be synthesized in 3 ways. They are:

1. Divergent method
2. Convergent method
3. Double exponential method

Divergent method: In this approach, the dendrimer develops from a core molecule. The core molecule reacts with monomer units containing one reactive and two dormant groups. This reaction gives out the 1st generation dendrimer. The formed new periphery of the first generation dendrimer is activated for further monomer reactions. This process is repeated for several generations until a desired generation dendrimer is built. Divergent approach of synthesis is useful for the production of large quantities of Dendrimers because with each generation adding step, the molar mass of dendrimer gets doubled. Problems encountered during the synthesis of Dendrimers are incomplete and side reactions of the end groups that lead to structural defects. In order to prevent the side reactions and to force the reactions towards completion, large quantities of reagents are required that in turn arise difficulty in the purification of the final product [12].

Convergent method: Convergent method was developed to overcome the problems faced during divergent synthesis. In this approach, the dendrimer is constructed stepwise from the end groups and slowly progress towards the core material. The growing branched polymeric arms are attached to the core molecule when the desired generation has been obtained. This approach has many advantages like:

- Purification of the desired product is easy and defects in the final structure can be minimized.
- Introduction of subtle engineering to the dendrimer structure is possible by precise placing of the functional groups at the periphery of the dendrimer molecule.

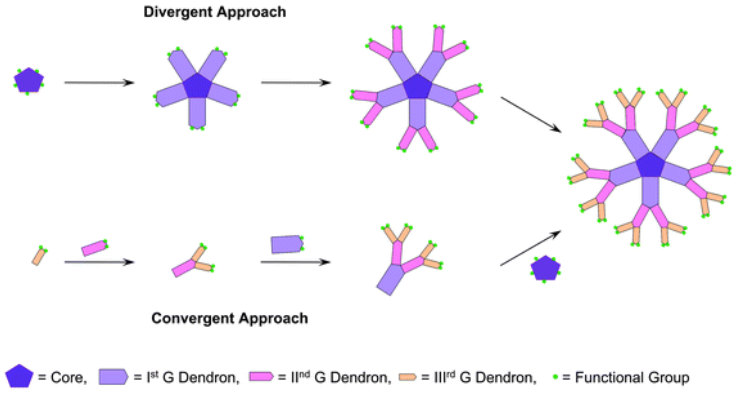

Fig. 3 Divergent and Convergent growth of Dendrimers

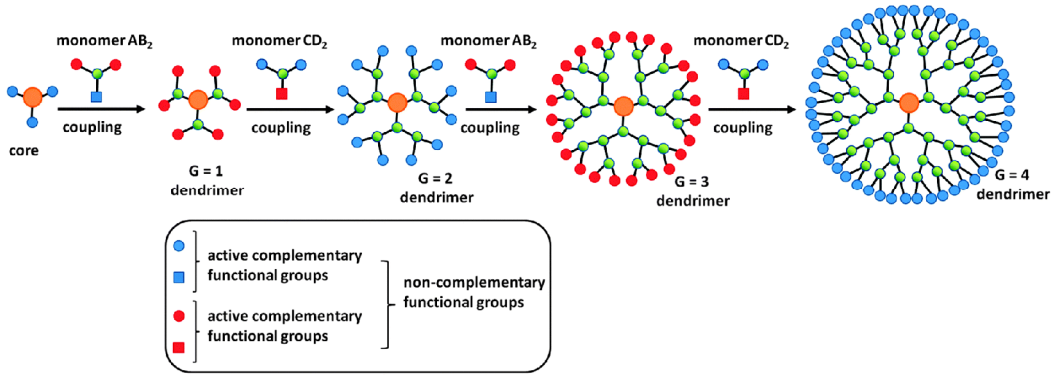

Fig. 4 Double exponential growth of Dendrimers

Double exponential / mixed growth:

Double exponential growth is a rapid growth technique for linear polymers. In this approach, monomers of both divergent and convergent growth are prepared from a single starting material. Then the two products are reacted together to give an orthogonally protected trimer, that repeats the growth process again. This approach provides a means where a dendrimer fragment can be extended either in divergent or convergent fashion [13].

DENDRIMER – DRUG INTERACTIONS

Dendrimer-drug interactions are necessary for encapsulating and eliciting the therapeutic activity. Dendrimer drug interactions are broadly divided into:

1. Simple encapsulation
2. Electrostatic interactions
3. Covalent conjugation
4. **Simple encapsulation:**

The presence of empty internal cavities makes Dendrimers suitable to encapsulate the guest molecules directly. The internal cavities are hydrophobic in nature and enable them to interact with the poorly soluble drugs through hydrophobic interactions. The nitrogen or oxygen atoms of the dendritic architecture interact with the drug molecules through hydrogen bonding, hydrophobic interactions and physical encapsulation.

5. **Electrostatic interactions:**

Presence of high density functional groups like amine and carboxyl groups on the dendritic surface enhances the solubility of hydrophobic drugs by electrostatic interactions.

E.g: G3 PAMAM Dendrimers with ammonia core NSAID's with carboxyl group like ketoprpfen, ibuprofen etc.,

interacts with Dendrimers electrostatically

6. **Covalent conjugation:**

Another way of interaction of Dendrimers with the guest molecules is covalent conjugation. Here the drug binds covalently to the dendritic surface (functional groups) and drug release occurs through the enzymatic or chemical cleavage of hydrolytic labile bonds.

Mechanism of drug delivery through Dendrimers: Because of the structural perfection of the Dendrimers, drugs can be loaded in both the interior as well as exterior of the dendritic structure. There are 2 mechanisms of drug delivery explored till now. They are:

a. In the presence of suitable enzymes/environment, drug-dendrimer covalent bonding degrades *invivo* and releases the drug at the site of action.
b. The second approach is- release of drug due to changes in the physical environment like pH, temperature etc. This approach is independent of the external factors and occurs in core cavities or outer shell receptors [14, 15].

CHARACTERIZATION OF DENDRIMERS:

Dendrimers are characterized by the following ways:

1. **Spectroscopic methods:** Widely used spectroscopic methods for the characterization of Dendrimers are:
    a. **NMR** – it is used to analyze the step by step synthesis of Dendrimers like analysis of size, morphology and dynamics of Dendrimers etc.
    b. **Mass spectroscopy** – In this method, small Dendrimers of molecular weight below 3000 Daltons are characterized by adapting techniques like chemical ionization and fast atom bombardment.
    c. **XRD** – Through XRD technique, we can accurately determine the chemical composition, shape, structure and size of Dendrimers.
    d. **UV-Visible** – it is used to monitor the synthesis of Dendrimers.
    e. **IR Spectroscopy** – Through IR, we can analyze the chemical transformations that occur at the surface of the Dendrimers.
    f. **Fluorescence** – it is used to quantify the defects during the synthesis of Dendrimers.
2. **Scattering techniques**: Some common scattering techniques used in the characterization of Dendrimers are:
    a. **Small angle X-ray scattering** – gives information regarding the arrangement of polymer segments within the dendrimer.
    b. **Small angle neutron scattering** – helps to obtain information regarding the internal structure and the location of end groups in the Dendrimers.
3. **Microscopy:** Electron microscopy and scanning electron microscopy are used to produce images of the synthesized dendrimer.
4. **Size Exclusive chromatography:** It allows the separation the molecules based on their size.
5. **Electrical techniques:**
    a. **Electrochemistry** – electrochemistry gives information regarding the active surface end groups interact with the drug molecules.
    b. **Electrophoresis** – it provides information about the purity and homogeneity of Dendrimers.
6. **Rheology and physical properties:**
    a. **Intrinsic viscosity** – it is an analytical probe that determines the morphological structure of the Dendrimers.
    b. **Differential scanning calorimetry** – through this technique, we can determine the glass transition temperature that further depends on the parameters like molecular weight, entanglement and composition of polymers [16].

APPLICATIONS OF DENDRIMERS:

1. **Ocular drug delivery:** Dendrimers provide unique solutions to ocular problems through effective ocular drug delivery

E.g.: PAMAM Dendrimers with its carboxylic or hydroxyl surface groups exhibit increased residence time in the eye with pilocarpine nitrate. Thus the bioavailability of Pilocarpine is increased significantly with PAMAM Dendrimers.

2. **Dendrimers in Gene transfection:** Now-a-days Dendrimers have become the routine vectors in Gene therapy. Amino-terminated PAMAM or PPI Dendrimers act as non-viral gene transfer agents and enhance the DNA transfection by endocytosis.

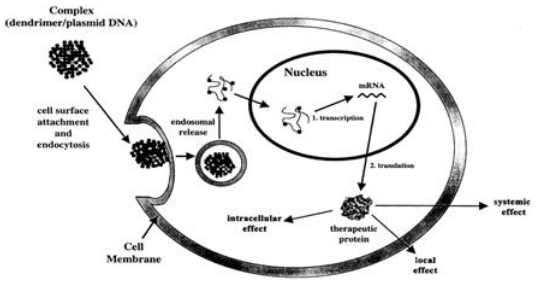

Fig. 5 Dendrimers in gene transfection

3. **As drug conjugates:** Dendrimers have the ability either to encapsulate the drugs internally or form conjugates by chemically interacting with the drugs at the dendrimer surface. The surface of the Dendrimers possesses some active sites where a drug molecule can bind through covalent bond formation. This conjugation helps in delivering the drug to the desired site effectively.
E.g.: PAMAM Dendrimers form conjugation with dyes; DNA strands etc., and exhibit desired therapeutic action [17].

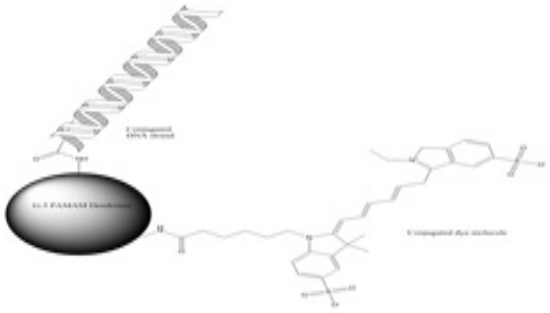

Fig. 6: Dendrimers as drug conjugate

4. Nano drugs:

Dendrimers are well suited for nano drugs. Nano particles are encapsulated within the dendrimer and carried to the target site to exhibit the desired therapeutic action.
Eg: Monodispersed nanodrugs can be synthesized using PPI or PAMAM Dendrimers with tertiary amine groups.

5. Imaging agents:

Dendrimers have evolved as an important tool in modern diagnostic medicine. Dendrimers can be used either as X-ray contrast agents or MRI contrast agents or as molecular probes. This wide range of application of Dendrimers is useful in the easy diagnosis of various diseases such as tumors etc. The distinct morphology and unique surface characteristics offer the Dendrimers to serve as imaging agents by providing various binding sites for their attachment.

6. Transdermal drug delivery:

Dendrimers suit precisely for the transdermal route of drug delivery. Dendrimers have the potential to enhance the permeation of the drug through the skin membrane. Thus the bioavailability of the drug is also increased.
Example: PAMAM Dendrimers forms complex with NSAIDs like Ketoprofen and Diflunisal. The formed complex exhibit 3 times higher permeation through the skin.

7. Solubility enhancers:

Dendrimers with its hydrophobic core and hydrophilic periphery can enhance the solubilization behavior of most of the drugs. Thus they are effective at delivering both hydrophobic and hydrophilic drugs to the target site. Example: PAMAM Dendrimers consist of internal cavities that can encapsulate hydrophobic drug molecules within it. Drugs can also be attached to the end groups of dendrimer surface, ultimately drug solubility and bioavailability is achieved [18].

8. Controlled drug release:

The encapsulation property offer Dendrimers to release the drug at a controlled manner to the target site.

Example: 5-fluoro uracil is encapsulated into PAMAM Dendrimers, produces controlled release of the drug to the target site with reduced toxicity [18].

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How to cite this article: B. Narasimha Rao*, V. Viswanath, K. Ravindra Reddy, S. Rahath Fathima , P. Surekha, S. Bhuvaneswari, Dendrimers – Structure, Synthesis, Encapsulation, Characterization and Applications, 6 (3): 2860 – 2866 (2015)