IJBPAS, June, 2021, 10(6): 1720-1732

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DENDRIMERS: A NOVEL APPROACH FOR TRANSLATIONAL RESEARCH

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Received 13th July 2020; Revised 11th Aug. 2020; Accepted 20th Sept. 2020; Available online 1st June 2021

https://doi.org/10.31032/IJBPAS/2021/10.6.5484

ABSTRACT

Dendrimers are highly branched molecules having a well-defined size, shape, molecular weight, and monodispersity as compared to a linear polymer. Dendrimer has a tree-like shape, consist of central core, branches and terminal group. The bioactive agents may either be encapsulated into the interior of the dendrimers or they may be chemically attached or physically adsorbed onto the dendrimer surface. Dendrimer has wide application in the pharmaceutical field, in gene transfection, as a diagnostic agent, as a blood substituent, as a solubility enhancer. Surface-modified dendrimers themselves may act as nano-drugs against tumours, bacteria, and viruses. This review focus on structure, property, method of synthesis, various method of characterization, application and formulation of dendrimers.

Key words: Dendrimers; Convergent; Divergent; applications; synthesis

INTRODUCTION

The term dendrimer coined from the Greek word 'Dendron' meaning a tree. The synonym for Dendrimer is 'Arborols' (from the Latin word 'arbor') also meaning a tree and 'Cascade molecule'. Dendrimers are repeatedly branched, globular, multivalent, monodisperse molecules with synthetic elasticity and possess well defined chemical structures **[1]**. Dendrimers having diameters in the 2 to 10 nm range. Dendrimer having very low polydispersity and high functionality. Dendritic polymers are recognized as the fourth major architectural class of polymers after the three well-known types (linear, cross-linked and branched polymers). They have

grown dramatically over about 27 years history **[2]**. The structure of a typical dendrimer is distinguished by three distinct characteristics namely; a central multifunctional 'core' generations ormultifunctional level of repeating unitsattached to the core and the terminal or end section. Manipulating these structural features of dendrimers allows the controlled synthesis of a whole series of highly branched end-functionalized macromolecules that are drawing increased attention for many potential applications **[3]**.

HISTORY OF DENDRIMERS

The first successful attempt to create and design dendritic structures by divergent synthesis was carried out by Fritz Vögtle and coworkers in 1978, **[4]** followed by R.G. Denkewalter at Allied corporation in 1981, **[5]**. Donald Tomalia at Dow chemicals in1983, and George Newkome in 1985, **[6]**. In 1990 Jean Frechet introduced the convergent synthetic approach. Although a lot of researchers have concluded work in studying the different properties and applications of dendrimers but another school of thought believes the research on the properties and applications of dendrimers is still in its infancy.

METHOD OF SYNTHESIS [7-15]

The classical polymerization process which results in linear polymers is usually random and produces molecules of different sizes, whereas the size and molecular mass of dendrimers can be specifically controlled during synthesis.

1. Divergent Method
2. Convergent Method
3. Double Exponential and Mixed Method
4. Hypercores and Branched Monomers Growth

Divergent Method:

The growth of dendrimers derived from a core-site. For the development of the core site 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 technique is repeated until the described size is obtained. By this approach, the first synthesized dendrimers were polyamidoamines (PAMAMs), also known as star-burst dendrimers. **Figure 1**.

Merit:- By this method large quantity of dendrimers are produced.

Demerit:- For the synthesis of a large quantity of reagent required to prevent the problem.

Convergent Method:

Dendrimers are constructed from the beginning of small molecules that end up at the surface of the sphere, and reactions precede inmost building inward and are eventually attached to a core. This method makes it very much easier to eliminate the impurities and shorter twigs along the way, so that the final dendrimer is more mono-

disperse. However, dendrimers ended this way are not as large as those made by divergent methods because crowding due to stearic property along the core is restrictive. **Figure 2**

Merit:- Defects in the final structure are less. The product easily purified.

Demerit:- Due to steric hindrance higher generation dendrimer cannot be formed.

Double exponential and mixed growth method

The double explanation method can basically be regarded as a covergent growth strategy for a Dendron, this approach involves growth of Dendron in two directions:

1. Growth inwards towards core by focal point activation and
2. Growth towards surface by surface group activation

A branching moiety containing two coupling sites both are completely protected undergoes selective deprotection. In two completely separate steps, branching unit in one step undergoes surface deprotection where as in other step it undergoes focal point deprotection.

Now both unprotected Dendron are reacted in second step to give second generation Dendron. Alteration of the synthetic sequence lead to the corresponding fourth generation Dendron. In this used both convergent and divergent methods **Figure 3**.

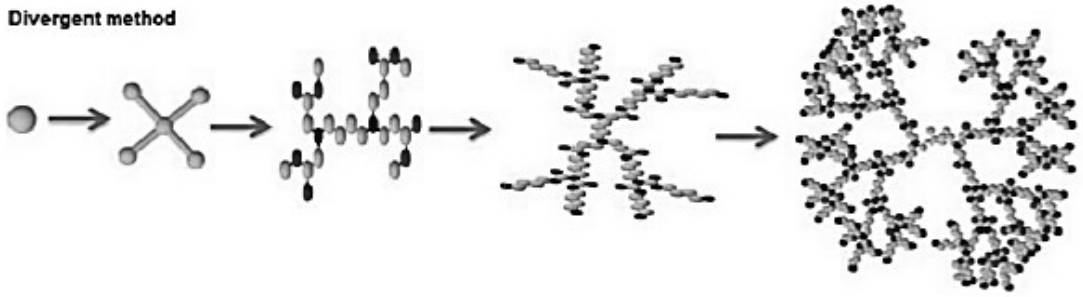

Figure 1: Divergent Method

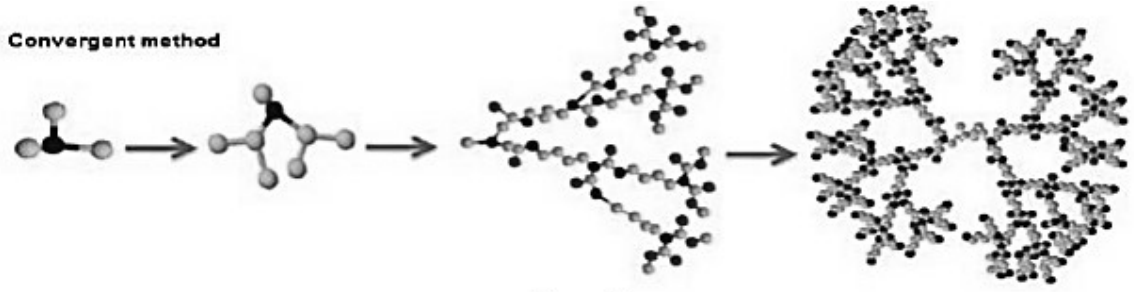

Figure 2: Convergent Method

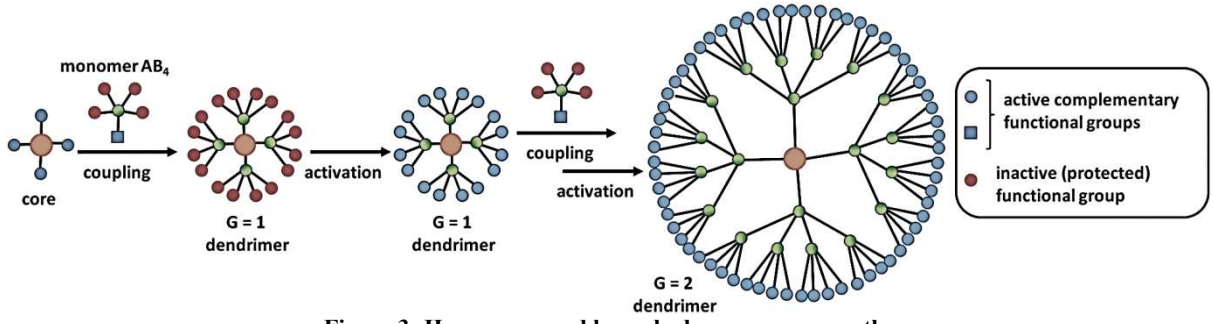

Figure 3: Hypercores and branched monomers growth

Characteristics

This method involved the pre-assembly of oligomeric species which can be connected together to give dendrimers.

FACTORS AFFECTING DENDRIMERS SYNTHESIS

Different factors can affect dendrimer synthesis. The non-ideal dendrimer expansion may be manifested through a variety of ways which includes:

1. Incomplete addition reaction.
2. Intermolecular cyclization.
3. Fragmentation.
4. Solvolysis of terminal functionalities.

CLASSIFICATION OF DENDRIMER [16]

Dendrimers can be classified based on their shape, structure, branching, solubility, chirality, and attachment, which are described in **Table 1**.

PROPERTIES OF DENDRIMERS

Tentatively, dendrimers are mono-dispersive. Due to small imperfection during the mechanized process, the polydispersity index is about 1.001. Polydispersity of 1.0007 for PAMAM has been report. Opposing to linear polymers, the viscosity will be reached with the maximum value that starts to decline **[17]**. The decline in viscosity is a result of prohibiting the interaction with the outer branches between molecules at a higher generation. Glass transition temperature (Tg) of dendrimers following similar trends. It reaches the maximum Tg and levels off at a higher molecular weight **[18]**. This behavior is the outcome of absence in embarrassment at higher molecular weights. Dendrimers differ from classical random coil molecules in that they are vastly branched, three-dimensional macromolecules with a branch point at each monomer unit. Several properties of dendrimer are listed below in the given **Table 2**.

Table 1: Classification of dendrimers [16]

S. No	Classification of dendrimer	Application/Method
1.	Simple Dendrimer	They have simple monomer units. The convergent synthesis of a sequence of monodisperse is old, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 and 46 benzene rings linked symmetrically and have molecular diameters of 45 A.
2.	Liquid crystalline dendrimer	These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer. Functionalization to the end group of carbosilane, dendrimers with 36 mesogenic units which can be attached through a C-5 spacer, and leads to liquid crystalline dendrimers that form broad smectic phase in the temperature range of 17°C to 130°C.
3.	Chiral dendrimer	In chiral dendrimers, the chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core e.g. chiral dendrimers obtained from pentaerythritol.
4.	Micellar dendrimer	These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a collection of an aromatic polymeric chain which able to generate an environment that resembles some micellar structures, which form a complex with small organic molecules in water.
5.	Hybrid dendrimers	These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. Which provides an opening to use them as surface-active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers.
6.	Amplhiphilic dendrimer	These are the class of globular dendrimers that have an asymmetrical but highly controlled division of chain-end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion.
7.	Metallo dendrimer	Dendrimers attached with the metal ion to form the complexation either in the interior or on the peripheral, which may be regarded as metallo dendrimers. The ruthenium bipyridine complex based dendrimer has attribute electrochemical and luminescence properties.

Table 2: Properties of dendrimers [19]

S.no	Property	Dendrimer
1.	Structure	Compact and Globular
2.	Shape	Spherical
3.	Architecture	Regular
4.	Structural control	Very high
5.	Synthesis	Stepwise growth
6.	Crystallinity	Non-crystalline and amorphous materials Lower glass temperatures
7.	Reactivity	High
8.	Aqueous solubility	High
9.	Nonpolar solubility	High
10.	Viscosity	Non-linear relationship with molecular weight
11.	Ionic conductivity	High
12.	Compressibility	Low
13.	Polydispersity	Monodisperse

TYPES OF DENDRIMERS:

(1) Radially layered poly amidoamine-organosilicon dendrimers (PAMAMOS)

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon-containing dendrimers. Consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent network regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, electronics, photonics, chemical catalysis etc. and useful precursors for the

preparation of honeycomblike networks with nanoscopic PAMAM and OS domains **[20, 21]**.

(2) Poly amidoamine dendrimers (PAMAM)

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. When looking at the structure of the high generation in two-dimensions, the star-like pattern observed. They are commercially available as methanol solutions and in generation G 0-10 with 5 different core types and 10 functional surface groups **[22, 23]**.

(3) Poly Propylene Imine dendrimers (PPI)

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary trispropylene amines present in the interior portion. It commercially available up to G5, and wide applications in material science as well as in biology **[24]**. PPI dendrimers are available as Asramol by DSM.

(4) Chiral dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to the chiral core. Their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.

(5) Liquid crystalline dendrimers

A highly-branched oligomer or polymer of a dendritic structure containing mesogenic groups that may show a mesophase behaviour. It consists of mesogenic (Liq. crystalline) monomers. e.g. mesogen functionalized carbosilane dendrimers.

(6) Tecto dendrimer

Tecto dendrimers consist of a core dendrimer, performing a variety of functions ranging from diseased cell identification, diagnosis of disease state drug delivery, reporting location and reporting therapy outcomes.

(7) Hybrid dendrimers

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

(8) Multilingual Dendrimers

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

(9) Micellar Dendrimers

Micellar dendrimers are unimolecular water-soluble hyperbranched polyphen-ylenes micelles.

APPLICATION OF DENDRIMER:

1.Pharmaceutical application

1.1Dendrimer in ocular drug delivery

Ideal ocular drug-delivery devices should be sterile, isotonic, non-irritating,biocompatible, does not run out from the eye and biodegradable **[25]**. Dendrimers offer innovative solutions to complex problems in the distribution of eye medicines **[26]**.

1.2 Dendrimers in pulmonary drug delivery

Dendrimers have been reported for the pulmonary drug delivery of Enoxaparin **[27]**.

1.3 Dendrimer in transdermal drug delivery

Dendrimers designed to be highly water-soluble and biocompatible can enhance the drug properties such as solubility and plasma circulation time through transdermal formulations and efficiently deliver medicines **[28]**.

1.4 Dendrimer in oral drug delivery-

Studies of oral drug delivery using the human colon adenocarcinoma cell line, Caco-2, showed that low-generation PAMAM dendrimers cross cell membranes **[29]**.

1.5 Dendrimers in targeted drug delivery

Dendrimers have ideal properties which are useful in the targeted drug-delivery system. Folic acid and Methotrexate are one of the most effective cell specific targeting agents delivered by dendrimers **[30]**.

1.6 Dendrimers for controlled release drug delivery

The anticancer drugs methotrexate and adriamycin were encapsulated into PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A third-generation dendritic unimolecular micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control **[31]**. Controlled release of Flurbiprofen could be achieved by the formation of a complex with amine-terminated generation 4 (G4) PAMAM Dendrimers **[32]**. The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to the unencapsulated drug.

1.7 Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as noncovalent complexes with drug molecules and hydrophobes, which are responsible for its solubilization behaviour **[33]**.

1.8 Cellular delivery using dendrimer carrier

Dendrimer–ibuprofen complexes rapidly reached the cells relative to the pure drug (1 hr versus>3 hr), indicating that dendrimers

can efficiently hold the complex drug within the cells **[34]**.

2. Therapeutic applications:

2.1 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 **[35]**. This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue.

2.2 Dendrimers for boron neutron capture therapy

Boron neutron capture therapy (BNCT) refers to the radiation generated from the capture reaction of low-energy thermal neutrons by 10B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. This radiation energy has been used successfully for the selective destruction of tissue. Dendrimers are very fascinating compound for use as boron carriers due to their well-defined structure and multivalency **[36]**.

3 Diagnostic applications

3.1 Dendrimers as molecular probes

Dendrimers are fascinating molecules to use as molecular probes because of their distinct morphology and unique characteristics. 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 **[37]**.

3.2 Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools in medicine and applies to numerous diseases. To obtain a high-resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent. Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Krause and co-workers synthesized several potential dendriticX-ray contrast agents using various organometallic complexes such as bismuth and tin **[38, 39]**.

3.3Dendrimers as MRI contrast agents

Several research groups have explored the use of dendrimers as a new class of high molecular weight MRI contrast agents. Wiener and co-workers developed a series of Gd (III)–DTPAbased PAMAM dendrimers **[40]**. To improve the pharmacokinetic properties of dendrimer contrast agents, the introduction of target-specific moieties to the dendritic MRI contrast agents have been considered. Wiener *et al* **[41]** synthesized folate conjugated Gd (III)–DTPA PAMAM

dendrimer, which increased the longitudinal relaxation rate of tumour cells expressing the high-affinity folate receptor.

Merits: [42, 43]

1. Dendrimers particle size in nanometer in range of 1- 100nm, hence easily crosses cell membrane.
2. Reduced clearance through the Reticulo – Endothelial System (RES) due to small size.
3. Dendrimer as a perfect carrier for an unstable drug which protected in the core.
4. It shows monodispersity.
5. Dendrimer improves the solubility of the poorly soluble drug.
6. Multiple functional groups are present on the outer surface of dendrimers, which can be used to attach vector devices for targeting to a particular site in the body.

Demerits: [44]

1. It is not suitable for oral drug delivery because the drug– dendrimer complex not crosses the gut wall.
2. Drug–dendrimer construct is considered a new chemical entity so that clinical testing for new construct required.

CONCLUSION

Due to their exclusive manner dendrimers have improved physical and chemical properties. The elevated stage of control over the structural design of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds as an ultimate carrier in a biomedical application such as drug delivery, gene transfection, and imaging. These properties construct the dendrimers a smart choice, for drug delivery application and improve the solubility of the poorly soluble drug. This review of dendrimer provides complete information about drug carriers, clearly identifies the prospective of this novel fourth building class of polymers‖ and confirms the high buoyancy for the future of dendrimers in the pharmaceutical field. These inimitable physical and chemical properties of dendrimer have demonstrated immense versatilities in a variety of applications. Also, further studies are needed to recognize their absorption, uptake mechanisms by biological membranes and *in-vivo* stability. Dendrimers have successfully used in medicinal applications such as diagnostic tools and ultimately in drug delivery.

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