AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Review on Fundamentals of Dendrimers

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ABSTRACT

This review gives concise information about physico-chemical properties, synthetic strategies, characterization and possible application of Dendrimers in drug delivery. Dendrimers also known as arborols. They are radially symmetric molecules having nano size with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. Due to their unique architecture these have improved physical and chemical properties. They are having terminal groups, due to which these show high solubility, miscibility and reactivity. The major applications of Dendrimers are: Gene and oligonucleotide delivery, Targeting of anticancer chemotherapy. Their compatibility with DNA, heparin and polyanions make them more versatile.

Keywords: Dendrimers, PEGylated dendrimers, PPI Dendrimer, PAMAM Dendrimer**,** PAMAMOS Dendrimer.

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Received 21 January 2015, Accepted 28 January 2015

Please cite this article as: Saindane HB *et al.*, Review on Fundamentals of Dendrimers. American Journal of PharmTech Research 2015.

INTRODUCTION

In 1978, Fritz Vogtle and co-workers, introduced dendrimer chemistry and in 1985[1], Donald A. Tomalia, synthesized the first family of dendrimers.[2] The term originates from 'Dendron' meaning a tree in Greek. At the same time, Newkome's group in 1985 independently reported synthesis of similar macromolecules.[3] 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. In 1990 a convergent synthetic approach was introduced by Jean Fréchet. Various problems like poor solubility, bioavailability, permeability, biocompatibility and toxicity can be overcome by Dendrimers. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular.[3, 4] Dendrimers having step by step controlled synthesis and it is made up of monomers due to this, they exhibits characteristics features of molecular chemistry as well as polymer chemistry respectively.[5]

Structure of Dendrimer[6]

Dendrimers are built from a starting atom such as nitrogen, which is called as core. To which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure, which is called as Generations. As the process repeats, successive layers of terminal functional groups are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure which is nothing but the dendrimer.[6]

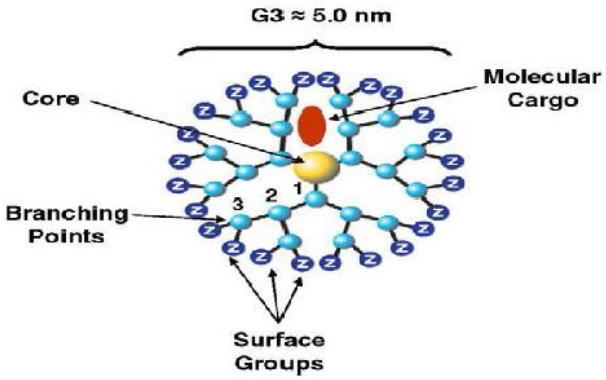

Figure 1: Structure of Dendrimer

Dendrimers possess three structural components such as:

I. Core: Molecular information region, size, shape, directionality and multiplicity

II. Interior: Branch cell amplification region

III. Surface: Reactive terminal groups (Templates polymerization region)

COMPONENTS OF A DENDRIMER STRUCTURE: [7]

Branching units:

It is the hyper branching when going from the center of the dendrimer towards the outward, resulting in homo structural layers between the focal points (branching points). The number of focal points when going from the core towards the dendrimer surface is the generation number. That is a dendrimer having five focal points when going from the center to the periphery is denoted as the 5th generation dendrimer.

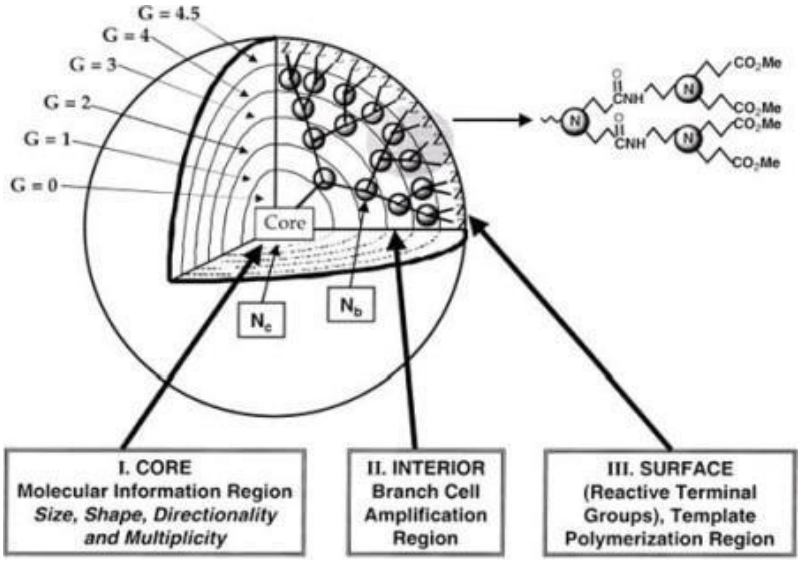

Figure 2: Components of Dendrimer

Shell

The dendrimer shell is the segment between the branching points and the "generation space". The "outermost shell" is the space between the last outer branching point and the surface. The dendrimer interior forms the "inner shell"

Pincer:

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

End-group

It is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimer having amine end-groups is termed "amino-terminated dendrimer".

TYPES OF DENDRIMERS[8, 9, 10, 11]

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[(9)] (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 star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

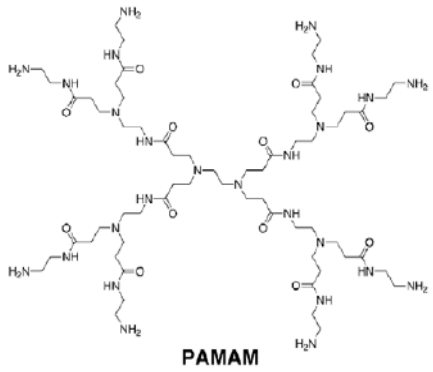

Figure 3: Structure of PAMAM Dendrimer

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.

PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle.[10] 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.

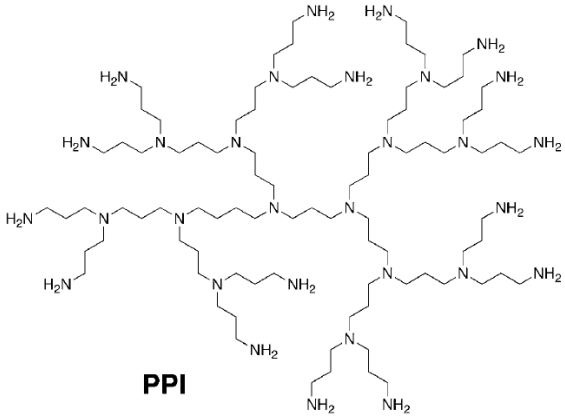

Figure 4: Structure of PPI Dendrimer

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.

Fréchet-type dendrimers

It is a more recent type of dendrimers developed by Hawker and Fréchet[10, 12] 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 fictionalization, and as polar surface

groups to increase the solubility of this hydrophobic dendrimers type in polar solvents or aqueous media.

Construction of dendrimers

Most syntheses of dendrimers involve the repetitious alternation of a growth reaction and an activation reaction. Often, these reactions have to be performed at many sites on the same molecule simultaneously. Clearly, the reactions must be very 'clean' and high yielding for the construction of large targets to be feasible. Many dendrimer syntheses rely upon traditional reactions, such as the Michael reaction, or the Williamson ether synthesis, whilst others involve the use of modern techniques and chemistry, such as solid-phase synthesis, organotransition-metal chemistry, organosilicon chemistry, organo-phosphorus chemistry, or other contemporary organic methodologies. The choice of the growth reaction dictates the way in which branching is introduced into the dendrimer. Branching may either be present in the building blocks as is more often the case or it can be created as a function of the growth reaction, as is the case with the PAMAMs and the poly (propylene imine)s. For details of the chemistry employed in the production of dendrimers, there are many comprehensive works which can be referred to by the reader[2, 13]

1. 'Divergent' dendrimer growth

The synthetic methodology employed in the early dendrimer syntheses came to be known as the 'divergent' approach. This name comes from the way in which the dendrimer grows outwards from the core, diverging into space. A schematic representation of divergent growth is shown in figure 3. Starting from a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers. The two steps can be repeated. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is doubled. Very large dendrimers have been prepared in this way, but incomplete growth steps and side reactions lead to the isolation and characterization of slightly imperfect samples[3]. Divergently grown dendrimers are virtually impossible to isolate pure from their side products. The synthetic chemist must rely on extremely efficient reactions in order to ensure low polydispersities.

2. 'Convergent' dendrimer growth

The 'convergent' approach was developed as a response to the weaknesses of divergent syntheses. A schematic representation of divergent growth is shown in figure 4.Convergent growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more monomers. When the growing wedges are large enough, several

are attached to a suitable core to give a complete dendrimer. The advantages of convergent growth over divergent growth stem from the fact that only two simultaneous reactions are required for any generation-adding step. Most importantly, this protocol makes the purification of perfect dendrimers simple. There are also certain other advantages associated with convergent growth. The growth reactions do not have to be so stringently efficient, and it becomes possible to introduce subtle engineering into the dendritic structure. This principle will be examined in detail in the next section. Convergent syntheses are not without their own shortcomings, however. The number of steps required to build up a large structure is not reduced compared with the divergent approach, yet a great deal more starting material is required. The convergent methodology also suffers from low yields in the synthesis of large structures. Dendritic wedges of higher generations encounter serious steric problems in the reactions of their 'focal points'.

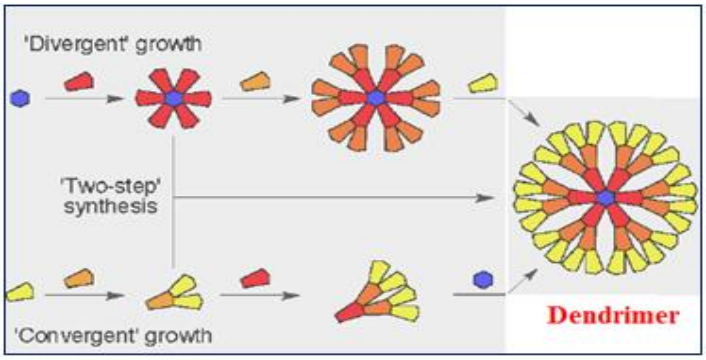

Figure 5: Construction of Dendrimer by Divergent and Convergent Growth

3. 'Hypercores' and 'Branched' monomers[14]

Hypercores and branched monomers allow the chemist to devise synthetic strategies that are more convergent in the classical synthetic sense of the word. An interesting comparison of convergent, divergent, and hypercore synthesis in the preparation of phenylacetylene dendrimers was attempted by Moore, but solubility problems in the divergent steps made the convergent approach favorable.

4. 'Double exponential' and 'Mixed' growth[15]

The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB2 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 as shown in figure 6.

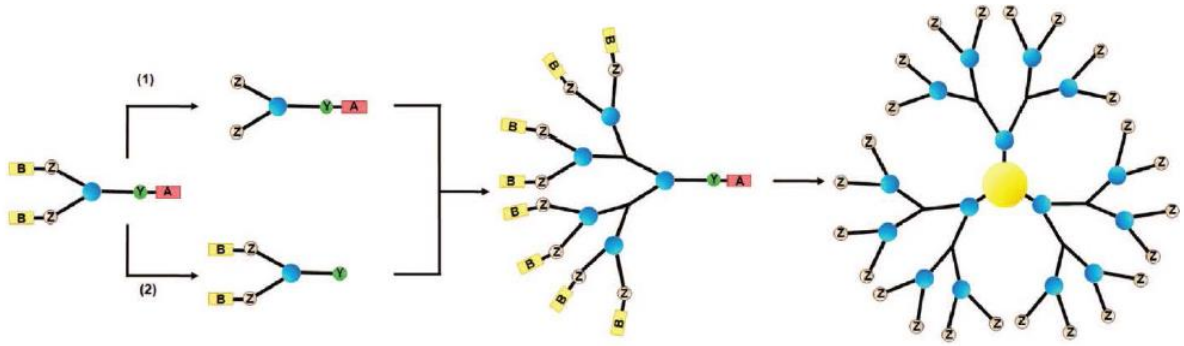

Figure 6: Process of Dendrimer construction by Double exponential and Mixed growth

ENCAPSULATION OF DRUGS WITHIN THE DENDRITIC ARCHITECTURE

Dendritic architecture (open nature) has led several groups to investigate the possibility of encapsulating drug molecules within the branches of a dendrimer. This offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability and controlling its release. The nature of drug encapsulation within a dendrimer may be simple physical entrapment, or can involve non-bonding interactions with specific structures within the Dendrimer.[22-24]

Unimolecular micelles

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. For example synthesized a symmetrical, four directional saturated hydrocarbon cascade polymer containing 36 carboxylic acid moieties with a neopentyl core. It was shown that lipophilic probes were located within the lipophilic infrastructure of the dendritic structures and it was concluded that the polymers exist as single molecules capable of molecular inclusion and therefore act as unimolecular micelles[26-29]

PEGylated dendrimers

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer to provide a hydrophilic shell around a hydrophobic dendritic core to form a unimolecular micelle. Because of its high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications. Liu et al., pentanol-based monomer was used to increase the flexibility and cavity size of the dendritic architecture by use of PEG[30-31]

Dendritic box

Jansen et al. described the synthesis of poly(propyleneimine) dendrimers based dendritic boxes. During the synthetic process, guest molecules could be entrapped within the cavities of the dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication. Through end group modification with a bulky amino acid derivative to yield a dense and rigid chiral shell with solid-phase properties and a flexible core capable of entrapping molecules[32,33].

Cored dendrimers

Zimmerman and co-workers synthesized cored dendrimers that resemble hollow nanospheres, encapsulate substances made them candidates for delivery vehicles. Encapsulation was achieved by postsynthetic modification of the dendritic architecture. The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups [34,35]

Methods for characterization of dendritic polymer[16]

The development of mass spectroscopic techniques such as MALDI and electrospray mass spectrometry has allowed the absolute determination of dendrimer perfection. Mass spectrometric results on dendrimers demonstrate the extreme sensitivity of the technique and the uniformity of the molecular mass. Scattering techniques measure the radius of gyration (Rg) of dendrimers, which is an average of the spatial distribution of all of the units. Transmission electron microscopy (TEM) has been used to image individual dendritic molecules, usually the larger generations. Recently atomic force microscopy (AFM) has also been used to image dendritic molecules.

Following methods can be used for characterization of dendritic polymers.

1. Spectroscopy and spectrometry methods like Nuclear Magnetic Resonance (NMR), Infra-red (IR) and Raman, Ultra-violet-visible (UV-VIS), Fluorescence, Chirality, Optical rotation, Circular dichroism (CD), X-ray diffraction, and Mass spectrometry
2. Scattering techniques like Small angle X-ray scattering (SAXS), Small angle neutron scattering (SANS), and Laser light scattering (LLS)
3. Electrical techniques like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis
4. Size exclusion chromatography (SEC)
5. Microscopy like Transmission electron microscopy, Scanning electron microscopy and atomic force microscopy
6. Rheology, physical properties like intrinsic viscosity, Differential Scanning Calorimetry (DSC), and Dielectric spectroscopy (DS)

7. Miscellaneous like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc.

Comparison of characterization of dendritically branched polymers by SANS, SAXS, and TEM

Small angle neutron scattering (SANS), small angle x-ray scattering (SAXS), and transmission electron microscopy (TEM) have been used to characterize the size, shape and interactions of dendrimers, hyper branched, and dendrigraft polymers. Size in terms of radius of gyration (Rg) from scattering and diameter from microscopy can be routinely measured. Five technologically important factors of dendritically branched polymers have been identified and measured.

Applications of dendrimers

- Delivery of anticancer drugs by dendrimers and dendritic polymers.
- Dendrimers in gene transfection.
- Dendrimer in drug delivery.
- Use of dendrimers to cross cellular barriers.
- Dendritic medical imaging systems.
- Dendrimers in photodynamic therapy.
- Dendrimers as solubility enhancer.
- New Dendritic Adhesives for Sutureless Ophthalmic Surgical Procedures.
- Dendrimers as Nano-Drugs

Several dendrimer based products have already been approved by the FDA and some in Phase II clinical trials.

Various dendrimer based products are –[25-27]

(1) Alert ticket for Anthrax Detection

(2) Priofect™, Priostar™ and Starburst for targeted diagnostic, therapeutic delivery for cancer cells.

(3) SuperFect for Gene Transfection

(4) Stratus CS for Cardiac Marker

(5) Vivagel for preventing HIV

CONCLUSION

The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight, thereby offering new

scaffolds for drug delivery. An increasingly large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. 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. The high level of control over the architecture of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds ideal carriers in biomedical applications such as drug delivery, gene transfection and imaging.

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