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Review Article

DENDRIMER: AN INNOVATIVE ACCEPTABLE APPROACH IN NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Dendrimer are repeatedly branched, roughly spherical large molecules. The name comes from the Greek word which translates to "tree". Dendrimers also referred to as the "Polymers of the 21st century". Dendrimers are a unique class of polymers which play an important role in emerging nanotechnology. Novel drug delivery is one of the most attractive potential applications of dendrimers. Structural advantages allow dendrimers to play an important role in the fields of nanotechnology, pharmaceutical and medicinal chemistry. As a result of their unique behavior dendrimers are suitable for a wide range of biomedical and industrial applications. This review briefly discusses the various aspects of dendrimers including properties, component of a dendrimers structure, different methods of synthesis of dendrimers, characterization and dendrimers based products and their use as pharmaceutical, therapeutic, diagnostic agent and their potential for applications in drug delivery such as carrier molecule, diagnostics reagent, dendrimers in ocular, pulmonary & gene delivery. However, dendrimers is currently the internationally accepted term. A dendrimers is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. As part of our recent surveys into patent trends in nanotechnology, we discovered an explosion in dendrimers patenting which should contribute to the momentum for their commercialization, particularly in nanotechnology. Rationally and precisely designed dendrimers based carriers may realize an accurate delivery of drugs to the target site and lead to an enhanced efficacy of drugs.

Keywords: Dendrimers, Polyamidoamine, Targeted drug delivery, Controlled release drug delivery.

INTRODUCTION

Dendrimers are repetitively branched molecules.[1,2] The name comes from the Greek word "δένδρον" (pronounced Dendron), which translates to "tree". Synonymous terms for dendrimer include arborols and cascade molecules. However, dendrimer is currently the internationally accepted term. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. The word Dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point. The difference between dendrons and dendrimers is illustrated in figure one, but the terms are typically encountered interchangeably.[3] The first dendrimers were made by divergent synthesis approaches by Fritz Vögtle in 1978[4] R.G. Denkewalter at Allied Corporation in 1981, Donald Tomalia at Dow Chemical in 1983 and in 1985,[5,6] and by George Newkome in 1985.[7] In 1990 a convergent synthetic approach was introduced by Jean Fréchet.[8] Dendrimer

popularity then greatly increased, resulting in more than 5,000 scientific papers and patents by the year 2005.

Components of A Dendrimer Structure[9]

Generation

It is the hyper branching when going from the centre of the dendrimer towards the periphery, 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 centre to the periphery is denoted as the 5th generation dendrimer. Here we abbreviate this term to simply a G5-dendrimer.The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented here "G0".

Shell

The dendrimer shell is the homo-structural spatial segment between the focal points, 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.

Pincer

In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface. In PPI and PAMAM dendrimers the number of pincers is half the number of surface groups (because in these dendrimers the chain divides into two chains in each focal point).

End-group

It is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "amino-terminated dendrimers (Figure 2).

Molecular Modeling of Dendrimers[10]

The conformation of dendrimer molecules in the solid state and in solution is still controversial. In particular, conflicting predictions on the shape of dendritic molecules have been made on the basis of theory and molecular modeling.

Sr. No.	Lower generation	Higher generation
1.	Polarity is high	Polarity decreases as generation increases.
2.	Open structure, size of encapsulation cavity is small.	Close and compact structure, size of cavity is large.
3.	Lower generation allows interaction with protein e.g. myoglobulin.	Higher generation does not allow interaction with protein due to closed structure.
4.	*In vivo* toxicity is not reported for 3rd and 5th generation PAMAM dendrimer.	*In vivo* toxicity is reported for 7th generation PAMAM dendrimer.
5.	*In vitro* toxicity of (PAMAM) dendrimer for 3rd and 5th generation is less.	*In vitro* toxicity of PAMAM dendrimer for 7th generation is more.

Sr. No.	Parameter	Dendrimer	Linear polymer molecules
1.	Glass transition temperature	Levels off at higher molecular weight dendrimer due to more end groups and less entanglements.	Levels off due to declining influence of the end group and more entanglement.
2.	Intrinsic viscosity	Intrinsic viscosity does not increase with molecular mass but reaches a maximum at certain dendrimer generation.	Intrinsic viscosity increases with molecular mass.
3.	Solubility	More solubility in organic solvents in comparison to analogous linear polymer.	Less solubility than analogous dendrimer in organic solvent.
4.	Reactivity	The debenzylation of the polyesters via catalytic hydrogenation is only possible.	Not possible.
5.	Hydrodynamic volume	Hydrodynamic volume of 5th generation polyether dendrimer is approx. 30% smaller than that of its linear analogue.	30% more.

Dendrimers vs. Conventional Polymers[10]

Dendrimers differ from classical random coil molecules in that they are highly branched three-dimensional macromolecules with a branch point at each monomer unit. Therefore they are potentially the most highly branched structures that exist. Dendrimers also differ from hyperbranched polymers. Hyperbranched polymers are also highly branched but their structure is neither regular nor highly symmetrical. Secondly, dendrimer are obtained by careful, stepwise growth of successive layers or generations but hyperbranched polymers are obtained in a single step by polycondensation of an X2 Y monomer that contains two reactive groups of type X and one of type Y. Functional groups X and Y are selected in such a way that they can react with each other to form a covalent bond. As molecular weight increases within a homologous series of dendrimers, the molecules undergo a transition from an extended to a globular shape. In case of classical linear polymers such as poly (styrene) the viscosity increases sharply with molecular weight. Analogy between dendrimers and linear polymers is presented in the table given above.

Synthesis of Dendrimer

One of the very first dendrimers, the Newkome dendrimer, was synthesized in 1985. This macromolecule is also commonly known by the name arborol. Figure 3 outlines the mechanism of the first two generations of aborol through a divergent route (discussed below). The synthesis is started by nucleophilic substitution of 1-bromopentane by triethyl sodiomethane tricarboxylate in dimethylformamide and benzene. The ester groups were then reduced by lithium aluminum hydride to a triol in a deprotection step. Activation of the chain ends was achieved by converting the alcohol groups to tosylate groups with tosyl chloride and pyridine. The tosyl group then served as leaving groups in another reaction with the tricarboxylate, forming generation two. Further repetition of the two steps leads to higher generations of arborol.[8] Poly (amidoamine) or PAMAM is perhaps the most well known dendrimer. The core of PAMAM is a diamine (commonly ethylenediamine), which is reacted with methyl acrylate, and then another ethylenediamine to make the generation-0 (G-0) PAMAM. Successive reactions create higher generations, which tend to have different properties. Lower generations can be thought of as flexible molecules with no appreciable inner regions; while medium sized (G-3 or G-4) do have internal space that is essentially separated from the outer shell of the dendrimer. Very large (G-7 and greater) dendrimers can be thought of more like solid particles with very dense surfaces due to the structure of their outer shell. The functional group on the surface of PAMAM dendrimers is ideal for chemistry, which gives rise to many potential applications.[7]

Methods for Synthesis of Dendrimers

Dendrimers can be considered to have three major portions: a core, an inner shell, and an outer shell. Ideally, a dendrimer can be synthesized to have different functionality in each of these portions to control properties such as solubility, thermal stability, and attachment of compounds for particular applications. Synthetic processes can also precisely control the size and number of branches on the dendrimer. There are two defined methods of dendrimer synthesis, divergent synthesis and convergent synthesis. However, because the actual reactions consist of many steps needed to protect the active site, it is difficult to synthesize dendrimers using either method. This makes dendrimers hard to make and very expensive to purchase. At this time, there are only a few companies that sell dendrimers; Polymer Factory Sweden AB commercializes biocompatible bis-MPA dendrimers and Dendritech is the only kilogram-scale producers of PAMAM dendrimers. Dendritic Nanotechnologies Inc., from Mount Pleasant, Michigan, USA produces PAMAM dendrimers and other proprietary dendrimers.

Divergent method

The dendrimer is assembled from a multifunctional core, which is extended outward by a series of reactions, commonly a Michael reaction. Each step of the reaction must be driven

to full completion to prevent mistakes in the dendrimer, which can cause trailing generations (some branches are shorter than the others). Such impurities can impact the functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small.[11]

Convergent method

Dendrimers are built from small molecules that end up at the surface of the sphere, and reactions proceed inward building inward and are eventually attached to a core. This method makes it much easier to remove impurities and shorter branches along the way, so that the final dendrimer is more monodisperse. However dendrimers made this way are not as large as those made by divergent methods because crowding due to steric effects along the core is limiting.[11]

Double Exponential and Mixed Growth

A schematic representation of double exponential and mixed growth. Double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. 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.[7] These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again.[12]

FACTORS AFFECTING DENDRIMERS SYNTHESIS[10]

There are various factors which affect dendrimer synthesis. The nonideal dendrimer growth may be manifested in a variety of ways including-

a) Incomplete addition reaction
b) Intermolecular cyclization
c) Fragmentation, and
d) Solvolysis of terminal functionalities.

Some dendrimer defect events (eg.dendrimer fragmentation) can influence the degree of monodispersity during dendrimer growth. This is especially true if fragments posses amine functions which may participate with the propagation sequencing agents to produce new but 'regressed dendrimer' entities. They are usually due to following reasons:

- Incomplete removal of reactant at each of generation sequences leads to polydispersity since residual reactant functions as an initiator core to produce 0.5 generation and subsequent lower generations.
- Exposure of dendrimers to higher temperature causes cyclization of dendrimers by Intermolecular reactions.
- The incomplete amount of sequencing agent may cause bridging of dendrimer or nonideal dendrimer formation.

TYPES OF DENDRIMERS[13-18]

Simple Dendrimers

They have simple monomer units e.g.poly (amidoamine) dendrimers composed of poly (amidoamine) segments named as "starburst" dendrimers. Tomalia 1st reported the synthesis of starburst dendrimers in 1985.

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, star like pattern observed. They are commercially available as methanol solutions and in generation G 0-10 with 5 different core type and 10 functional surface groups. Dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core.

Poly (Propylene Imines) Dendrimers (PPI)

Poly (Propylene Imines) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary tris-propylene amines present in interior portion. It 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.16 PPI dendrimers, are available as Astramol TM.

Chiral Dendrimers

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

Liquid Crystalline Dendrimers

A highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour. They consist of mesogenic (liq. crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers.

Tecto Dendrimer

This class of polymer, composed of a central dendrimer with multiple dendrimers attached at its periphery, holds promise for multidrug delivery and environmental remediation applications.

- Diseased cell recognition
- Diagnosis of disease state
- Drug delivery
- Reporting location

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.

Multilingual Dendrimers

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

Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

Peptide Dendrimers

Dendrimers having peptides on the surface of the traditional dendrimer framework and dendrimers incorporating amino acids as branching or core units are both defined as 'peptide dendrimers'. Peptide dendrimers can be used as drug delivery, contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and sera diagnosis.

Amphiphilic Dendrimers

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

Frechet-Type Dendrimers

Frechet-Type Dendrimers 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.

CHARACTERIZATIONS OF DENDRIMER BY VARIOUS METHODS

Spectroscopy Techniques[19-24]

- **Ultra-violet-visible spectroscopy (UV-VIS)** Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units.
- **Infra red spectroscopy (IR)** for routine analysis of the chemical transformations occurring at the surface of dendrimers.
- **Near infra red spectroscopy** Used to characterize delocalize π-π stacking interaction between end groups of modified PANAM.
- **Nuclear Magnetic Resonance (NMR)** Analysis in step by step synthesis of Dendrimer. To Probe the Size, Morphology and Dynamics of Dendrimers for organic dendrimers such as PPI etc.
- **Fluorescence** The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers.
- **Raman spectroscopy** Give relevant information about the degree of cyclodehydrogenation of polyphenylene

dendrimers, and the characterization of PPI and phosphorus dendrimers.

- **Mass spectroscopy** Chemical ionization or fast atom bombardment can be used only for the characterization of small dendrimers whose mass is below 3000 Da. Electrospray ionization can be used for dendrimers able to form stable multicharged species.
- **X-ray diffraction (XRD)** This technique should allow precise determination of the chemical composition, structure, size and shape of Dendrimer.

Scattering Techniques[25, 26]

- **Small angle X-ray scattering (SAXS)** gives information about their average radius of gyration in solution. The intensity of the scattering as a function of angle also provides information on the arrangement of polymer segments, hence on the segment density distribution within the molecule.
- **Small angle neutron scattering (SANS)** gives access to the radius of gyration, but may also reveal more accurate information than SAXS about the internal structure of the entire dendrimer. The location of the end groups has also been determined by SANS experiments conducted with PAMAM dendrimers and PPI dendrimers having labeled (deuterated) or unlabelled end groups.
- **Laser light scattering (LLS)** to determine the hydrodynamic radius of dendrimers. Dynamic LLS is mainly used for the detection of aggregates.

Microscopy Methods[27]

- **Transmission microscopy** Electron or light produce images that amplify the original, with a resolution ultimately limited by the wavelength of the source
- **Scanning microscopy** The image is produced by touch contact Q at a few angstroms of a sensitive canilever arm with sample. Ex. Atomic force microscopy.

Chromatography[28]

Size exclusive or gel permeation chromatography allows the separation of molecules according to size

Electrical Techniques[29-33]

- **Electron paramagnetic resonance (EPR)** Quantitative determination of the substitution efficiency on the surface of PANAM dendrimers.
- **Electrochemistry** Gives information about the possibility of interaction of electroactive end groups.
- **Electrophoresis** used for the assessment of purify and homogeneity of several type of water soluble dendrimers.

ADVANTAGES OF DENDRIMERS[1,10,17]

- Dendrimers show a structural uniformity and monodispersity.
- Dendrimers have a better/greater targeting efficiency due to the presence of reactive functional groups on the surface of dendrimer. Terminal groups may also be modified to reorganize specific receptors.
- The surface modification may allow designing dendrimers mimicking biological exo-receptors, substrates, inhibitors or cofactors.
- The similarity of dendrimers structure with IgM antibodies (pentamers radially distributed) suggest that they may be used to function as antibodies e.g. activation of macrophages, recognition, and high affinity to antigen.
- Dendrimers have the ability to deliver drug inside the cell or they may improve intracellular trafficking.
- Dendrimers have s capability to entrap a variety of drugs having different types of functional groups in internal hollow core or by charge interactions.
- Dendrimers can be made stimuli responsive.
- Dendrimers have limited toxicity and immunogenicity but good biodegradability.
- They have better colloidal, biological and shelf-stability.

- They may be intrinsically anticancer agents in nature due to interferon, tumour necrosis factor including properties of acrylates.

CURRENT AND POTENTIAL APPLICATION OF DENDRIMERS[2, 34-36]

- Delivery of:
  - Nucleic acids
  - Encapsulated drug
  - Covalently linked drug
- Film forming agent for controlled release
- Lubricants for pharmaceutical processing
- New carrier system for drug delivery
- Inkjet Inks & Toners
- Diagnostic reagent in
  - Dendrimers as Serodiagnosis
  - Dendrimers as Biosensor system
  - Dendrimers as Resonance imaging
  - Dendrimers as molecular probes
  - Dendrimers as X-ray contrast agents
  - Dendrimers as MRI contrast agents
  - Dendritic Catalysts / Enzymes
  - Dendrimers as *In vitro* diagnostics
- Vaccines against bacteria, viruses & parasites
- Dendrimer in ocular drug delivery
- Dendrimer in transdermal drug delivery
- Dendrimers in pulmonary drug delivery
- Dendrimers in gene delivery
- Dendrimers as bio mimetic artificial proteins
- Dendrimers as nano-scaffolds
- Dendrimer as solubility enhancer
- Therapeutic application
- Dendrimers in photodynamic therapy (PDT)
- Dendrimers for boron neutron capture therapy (BNCT)

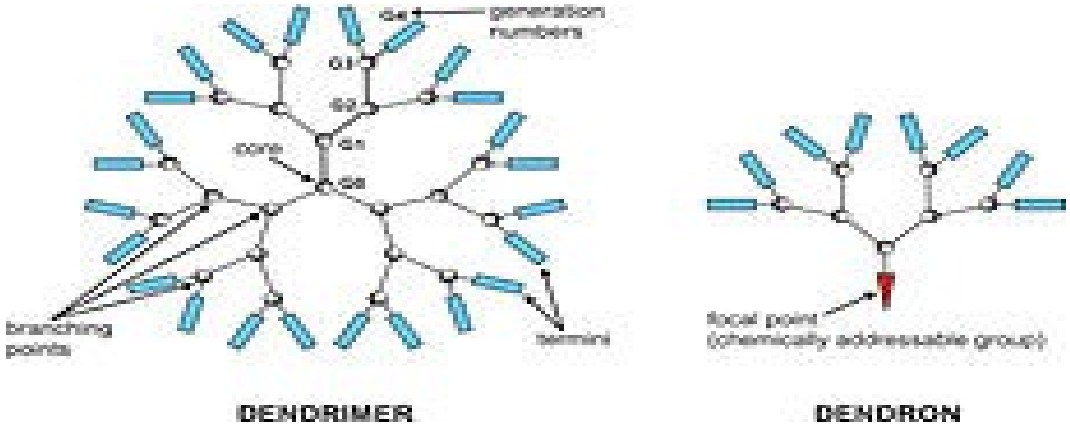

Figure 1: Dendrimer and Dendron

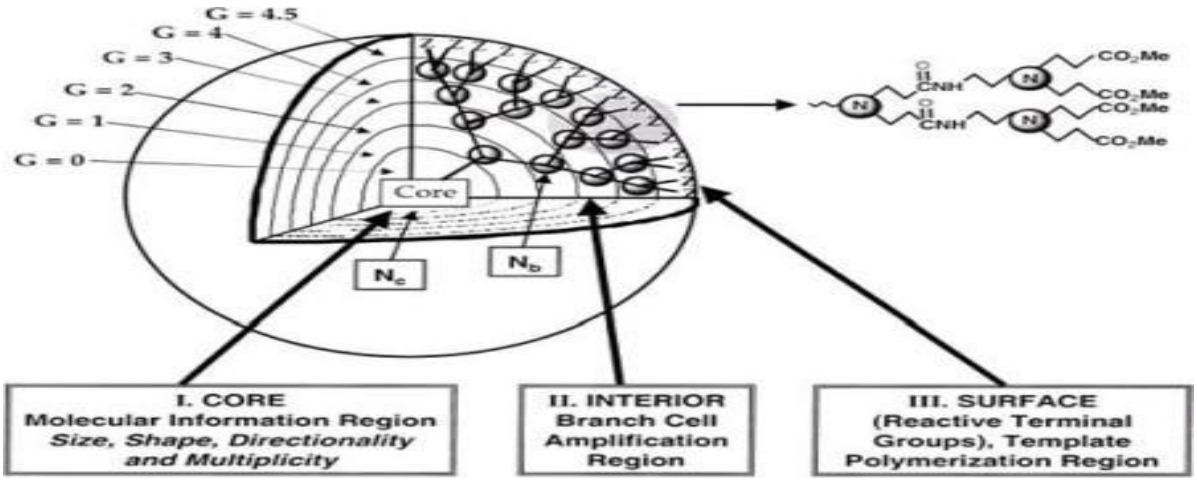

Figure 2: Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface

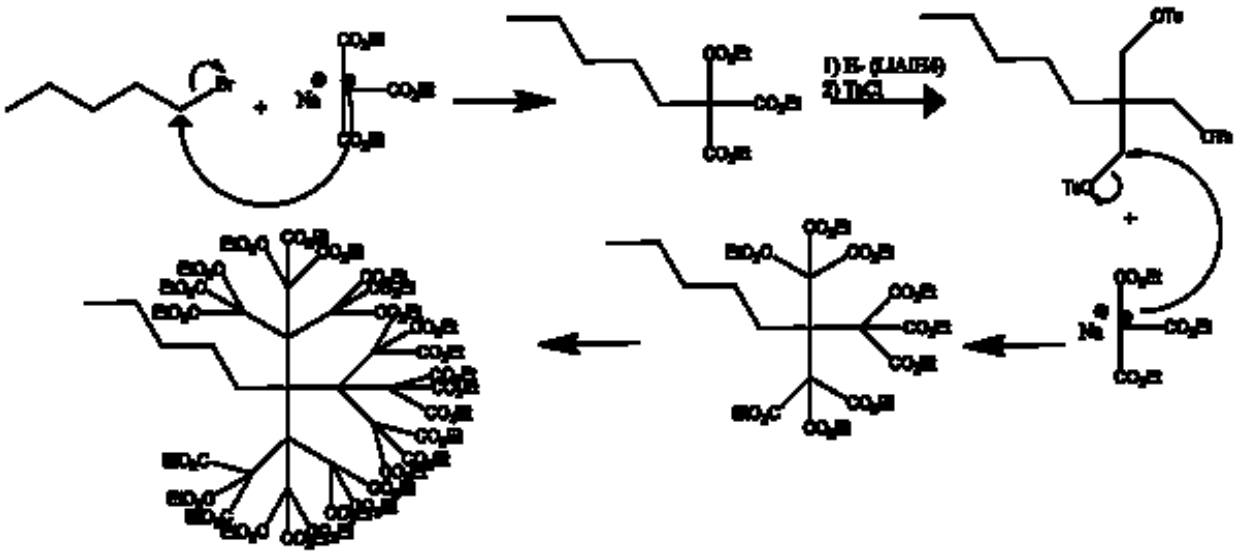

Figure 3: Synthesis to second generation arborol

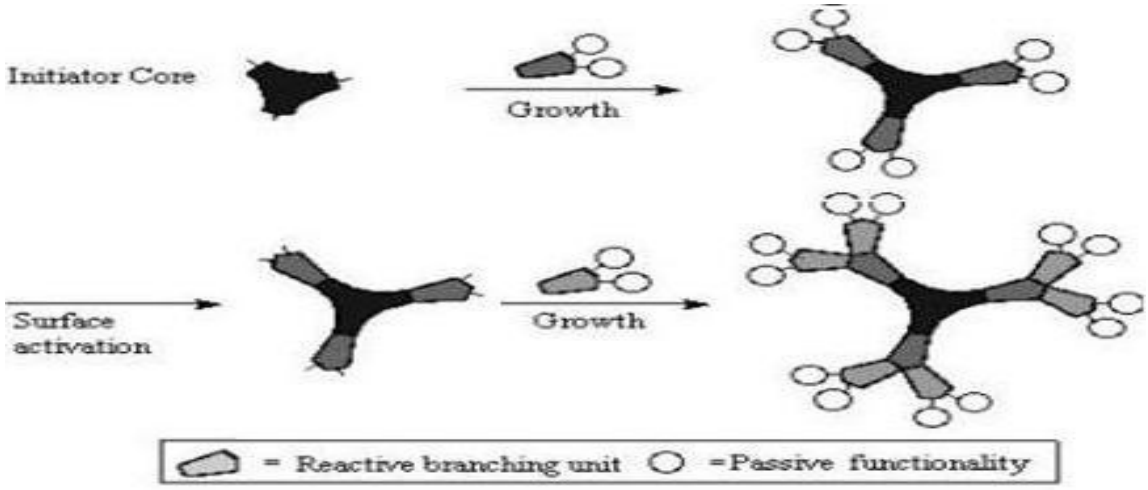

Figure 4: Schematic of divergent synthesis of dendrimers

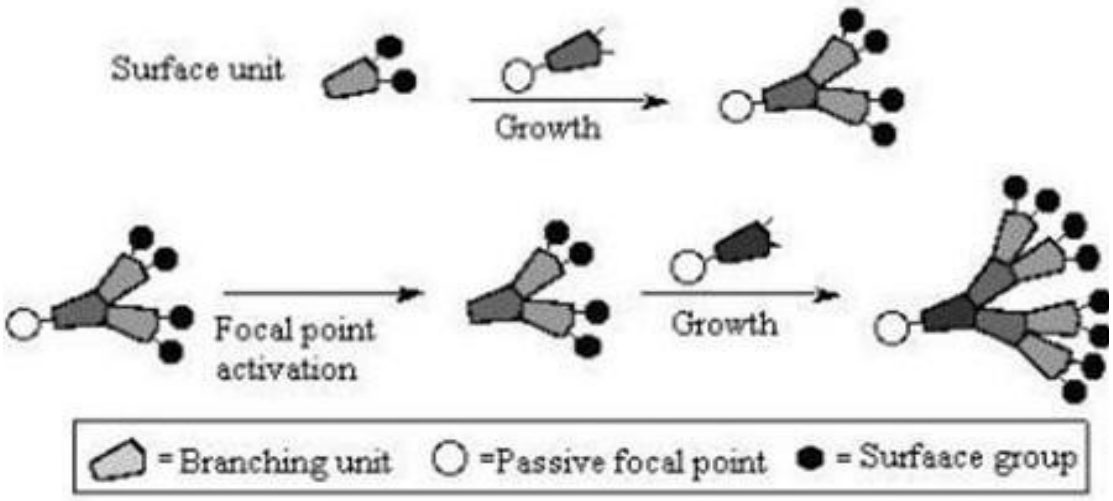

Figure 5: Schematic of convergent synthesis of dendrimers

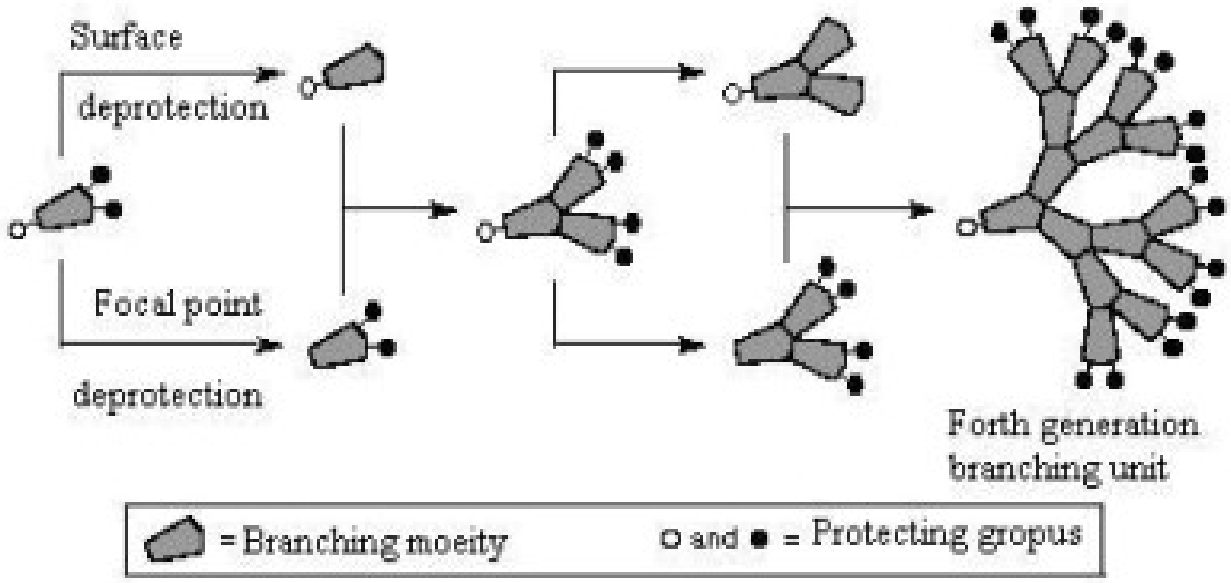

Figure 6: Double Exponential and Mixed Growth

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