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REVIEW ARTICLE

DENDRIMER: NOVEL STRATEGIES FOR DRUG DELIVERY SYSTEM

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Abstract:

The development of novel particulate systems with defined shapes and sizes is of prominent interest in certain therapeutic applications such as drug delivery, gene transfection, diagnostic and imaging. On controlling and designing optimized architectural design of dendrimers; their shape, size, branching pattern length/density, and their surface functionality, clearly discriminate these structures as inimitable and optimal hauler in those applications. Moderately modified dendrimers have been shown to act as nano-drugs adjacent to tumors, viruses and bacteria. Recent triumph in simplifying and optimizing the production of dendrimers make available a large variety of structures while simultaneously reducing the cost of their production. The reflections on biomedical applications of dendrimers given in this review clearly make obvious the impending of this new fourth major class of polymer structural design and undeniably prove the high expectation for the future of dendrimers.

Key words: Novel particulate systems, Dendrimers, gene transfection.

INTRODUCTION

A suitable drug delivery system would protect the drug against degradation and ensure that drug reaches proper permeability properties and further provides a combined transportation and protection system against the natural barriers, as done by the dendrimers. Dendrimers are highly defined nanoparticles: [1-4]

- Size: 1 -15 nanometers
- Very versatile surface functionalisation
- Synthetic: Practical and cost effective
- Well tolerated pharmaceutica.

Dendrimers are hyper-branched, globular monodisperse, three dimensional nanoscale synthetic polymers, having very well defined size, shape and definite molecular weight.[5] The term originates from 'dendron' meaning a tree in Greek. First discovered in the early 1980's by Donald Tomalia and co-workers,[1] these hyperbranched molecules were called dendrimers. The dendrimers are also called as CASCADE MOLECULES or ARBOROLS.

Dendrimers are hyper-branched, globular, monodisperse, three dimensional nanoscale synthetic polymers, having very well defined size, shape and definite molecular weight.Dendrimer is a nanoparticle (10^{-9}) and so has advantages over microparticles or others due to its small size, easy uptake by cells (through endocytosis).[6-7]

They are branched macromolecules have a central core unit having a high degree of molecular uniformity, narrow molecular weight, distribution, specific size and shape characteristics, and a highly- functionalized, terminal surface. Dendrimers exhibit characteristics features of both molecular chemistry and polymer chemistry. Molecular chemistry like properties are due to their step by step controlled synthesis while it shows polymer chemistry like properties as it is made up of monomers.[3]

Goals behind developing the dendrimers:

A) Modify/Improve the pharmacokinetic and pharmacodynamic properties of a drug so that there is also an accretion in bioavailability.

B) Achieve the controlled and targeted release of drug restricted to the area desired. [2]

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 that produce a spherical branching structure.[8]

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.[9]

Dendrimers possess three distinguished architectural components namely (figure 1)

I. Initiator core

II. Interior layers (generations) composed of repeating units, radically attached to the interior core.

III. Exterior (terminal functionality) attached to the outermost interior generations

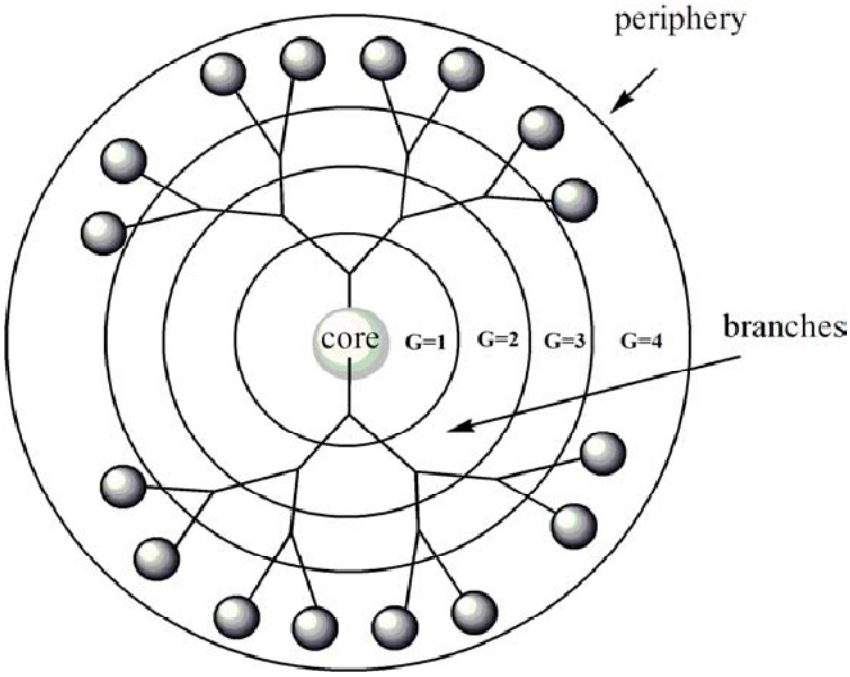

Figure 1: Schematic representation of the dendrimer typical structure.

Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymeriza- tion process which results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.[10-11]

Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers.

In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solutions have signifi- cantly lower viscosity than linear polymers.[12] When the molecular mass of dendrimers in- creases, their intrinsic viscosity goes through a maximum at the fourth generation and then be- gins to decline.[13] Such behaviour is unlike that of linear polymers. For classical polymers the intrinsic viscosity increases continuously with molecular mass.

The presence of many chain-ends is responsible for high solubility and miscibility and for high re- activity.[12] Dendrimers' solubility is strongly in- fluenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester. A marked differ- ence was also observed in chemical reactivity. Dendritic polyester was debenzylated by catalytic hydrogenolysis whereas linear polyester was unreactive.[14]

Lower generation dendrimers which are large enough to be spherical but do not form a tightly packed surface, have enormous surface areas in relation to volume (up to 1000 m^2/g).[5]

Dendrimers have some unique properties be- cause of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior.

Meijer and co-workers[14,15] trapped small molecules like rose bengal or p-nitrobenzoic acid inside the 'dendritic box' of poly(propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting the terminal amines with an amino acid (L-phenylalanine) and guest mole- cules were stably encapsulated inside the box. Hydrolysing the outer shell could liberate the guest molecules. The shape of the guest and the architecture of the box and its cavities deter- mine the number of guest molecules that can be entrapped. Meijer's group described experiments in which they had trapped four molecules of rose bengal or eight to ten molecules of p-nitrobenzoic acid in one dendrimers (figure 2).

ADVANTAGES [16-17]

- Medication to the affected part inside a patient's body directly
- Controlled and sustained release of drugs can also be obtained
- Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation
- Bypassing the gastric medium and hence the eschewing the variation due to effect of gastric secretions.
- Increase in therapeutic efficacy, decrease in side effects: decreased clearance of drug via altered distribution of drug in organs at site of localization and transportation due to controlled and sustained release of the drug.

- Relatively high drug loading.
- Preservation of drug activity: as drugs can be incorporated into the systems without any chemical reaction.

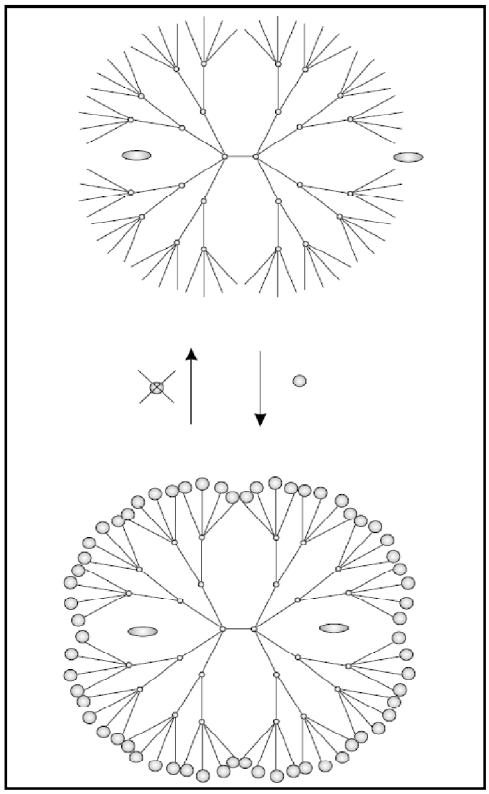

Figure 2: Dendritic structure showing cavity to adapt guest molecule

It is possible to create dendrimers which can act as extremely efficient light-harvesting antennae.[17,18] Absorbing dyes are placed at the periphery of the dendrimer and transfer the energy of light to another chromophore located in the core. The absorption spectrum of the whole macro- molecule is particularly broad because the peripheral chromophores cover a wide wavelength range. The energy transfer process converts this broad absorption into the narrow emission of the central dye. The light harvesting ability in- creases with generation due to the increase in the number of peripheral chromophores. Table 1 shows comparative study on the structure and adaptability of dendrimer and linear polymers.

Table 1: Properties of dendrimer and linear polymers [11-12, 19]

S.no.	Property	Dendrimers	Linear Polymers
1	Structure	Compact and Globular	Not compact
2	Shape	Spherical	Random coil
3	Architecture	Regular	Irregular
4	Synthesis	Stepwise growth	Single step polycondensation
5	Crystallanity	Non-crystalline and amorphous Materials Lower glass temperatures	Semi crystalline/crystalline Materials -Higher glass temperatures
6	Aqueous solubility	High	Low
7	Nonpolar solubility	High	Low
8	Compressibility	Low	High

TYPES OF DENDRIMERS

Various classes of dendrimers are classified as per their application in drug delivery of therapeutic moieties and their desired qualities (table 2).

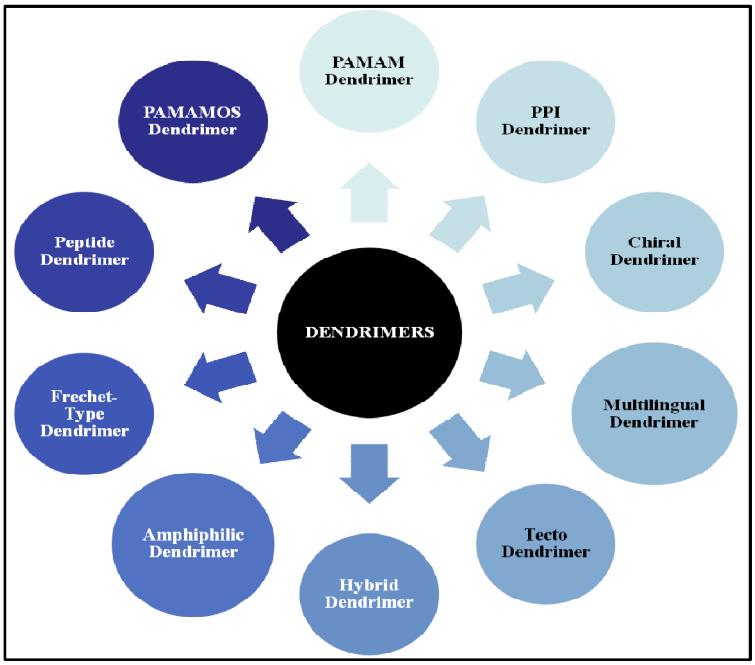

Figure 3: Various classes of Dendrimers

PAMAM Dendrimers [Poly (Amido Amine)]: PAMAM dendrimers are spheroidal or ellipsoidal in shape. These are most studied macromolecules and are commercially available.[7] The divergent method is used for their synthesis where ammonia or ethylenediamine is used as a starting material. The high solubility and reactivity of these are due to presence of a number of functional end groups and empty internal cavities [8-10]. The conventional macromolecules have low amino group density as compared to Pamam dendrimers.[20]

PPI /POPAM Dendrimers: PPI means Poly (Propylene Imine)/ Poly (Propylene Amine). [11] Its core structure is based on Diamino butane with primary amines as end groups and tertiary -propylene amines as interior. These are commercially available up to G-5 and are widely used in material science and biology.

Chiral Dendrimers: The chirality of the dendrimers are based upon the construction of constitutionally different but chemically similar branches to chiral core.[11]

Multilingual Dendrimers: These are the dendrimers which contain multiple copies of a particular functional group on their surface.[12]

Tecto Dendrimers: These are made up of core dendrimers which is surrounded by other dendrimers, each one of which perform a specific function leading to a smart therapeutic system which can simultaneously diagnose the diseased state and deliver API to the recognized diseased cell. [21]

Hybrid Dendrimers: These dendrimers have characters of both dendritic and linear polymer.[12]

Amphiphilic Dendrimers: These have one half that is electron donating and another half is electron withdrawing.

Peptide Dendrimers: Peptide dendrimers are those which contain amino acid as branching or interior unit. These are used for diagnostic purpose and vaccine delivery.[14, 22]

Frechet-Type Dendrimers: These are based on polybenzyl ether hyper branched skeleton. Carboxylic acid group found upon the surface of dendrimers which provides site for further functionalization and also enhance the solubility of dendrimers.[14]

PAMAMOS Dendrimers [Poly(Amidoamine- Organosilicon)]: These are silicon containing first commercial dendrimers. These are inverted unimolecular micelles that contain exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamin.[17]

Table 2: Types of dendrimers [20-26]

Types	Definition	Synthesis	Example	Applications
Pamam Dendrimer	Poly (amidoamine) dendrimers possess amino groups on the Surface.	Divergent	Dendritech (USA)	Material Science and Biomedicine Computer toners
Pamamos Dendrimer	Inverted unimolecular micelles consists of hydrophilic nuclephilic PAMAM interiors and hydrophobic organosilicon(OS) Exteriors.	Convergent and Divergent	SARSOX	Nano-lithography Electronics, Photonics Chemical catalysis Precursor for honeycomb like network preparations.
PPI dendrimer	Poly-alkyl amines having primary amines as end groups and its Interior consists of numerous tertiary trispropylene amines.	Divergent	Asramol by DSM (Netherlands)	Material science and biology
Tecto dendrimer	Composed of a core dendrimer with multiple dendrimers at its periphery	Divergent	Stratus® CS Acute Care TM, Starburst® , Mercapto	Diseased cell recognition Diseased state drug delivery diagnosis Reporting location to outcome of therapy
Amphiphilic dendrimers	Unsymmetical globular dendrimers built with two segregated sites of chain end.	Divergent	SuperFect, Hydraamphiphiles And bola-amphiphiles	Structure-directing agent, Use as polar part, cell and gene transfection.

Micellar dendrimers	Unimolecular micelle structure of Water soluble hyperbranched polyphenylene	Divergent	Beclometha zone dipropionat e, NX-200, Magnevist®	Biological and medical applications,Drug delivery, Imaging agent.
Multiple antigen peptide dendrimers	Dendron-like molecular construct based upon a polylysine skeleton.	Convergent	VivaGel	Used in vaccines and diagnostic research. Biological applications.
Frechettype dendrimers	Dendrimes having carboxylic acid groups as surface groups and containing poly-benzyl ether hyperbranced skeleton.	Convergent	Frechet type dendron azides, Priostar	Drug carrier, Purifiers, Organic synthesis, detecting agent, drug delivery.
Liquid crystalline dendrimers	Consists of mesogenic monomers	divergent	Polycanter liquid crystals, Mesogen functionaliz ed Carbosilane dendrimers	Science and Engineering.
Metallo dendrimers	Dendrimers with incorporated metal atoms	Convergent	Zinc Porphyrin dendrimers(M=Zn)	Sensing Catalytic applications, mimic biomolecules, lightharvesting, Biomarkers.

Synthesis of Dendrimers: These are synthesized by these methods:[15]

Dendrimers are synthesize by various methods but the methods shown in figure 4 are most commonly used and successful method for high yield dendrimers production.

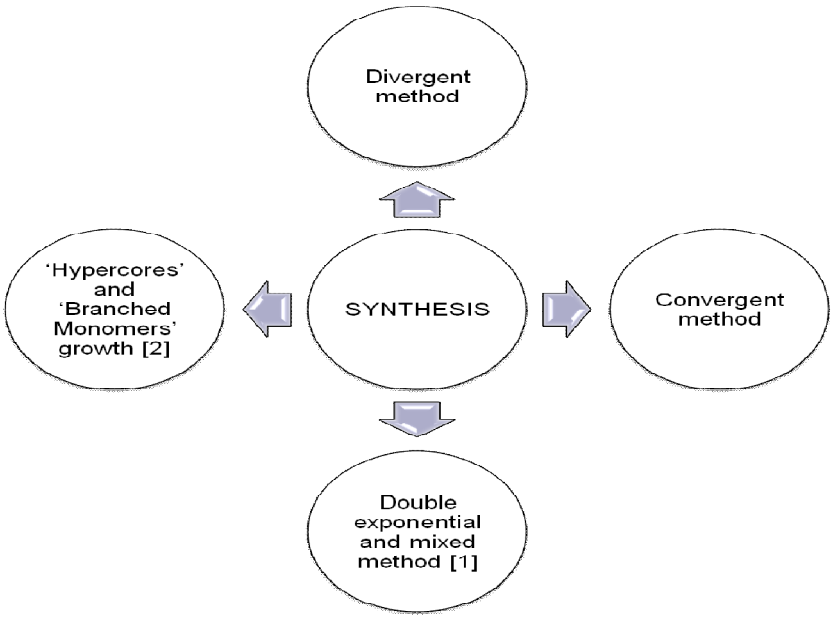

Figure 4: Methods for synthesis of dendrimers

Divergent Synthesis

Divergent synthesis is initiated with a multifunctional core molecule like ethylenediamine (EDA), then with the help of Michael addition reaction four arms are added on nitrogen of EDA (two arms possible on each nitrogen), after this in second step EDA is again reacted on these formed four arms through amidation reaction. These two steps can be repeated multiple times to form different generations of dendrimers, in each generation number of arms doubles from previous generation.

To avoid structural defects at higher generations a large excess of Michael donor (EDA) is used in this approach. This divergent route [27] is advantageous to get higher yield ofdendrimer with lower purity [22] or we can say that purity is compromised for getting higher yield. That's why this approach of synthesis is very useful and used worldwideat commercial scale for production of dendrimers.

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 (Figure 5).

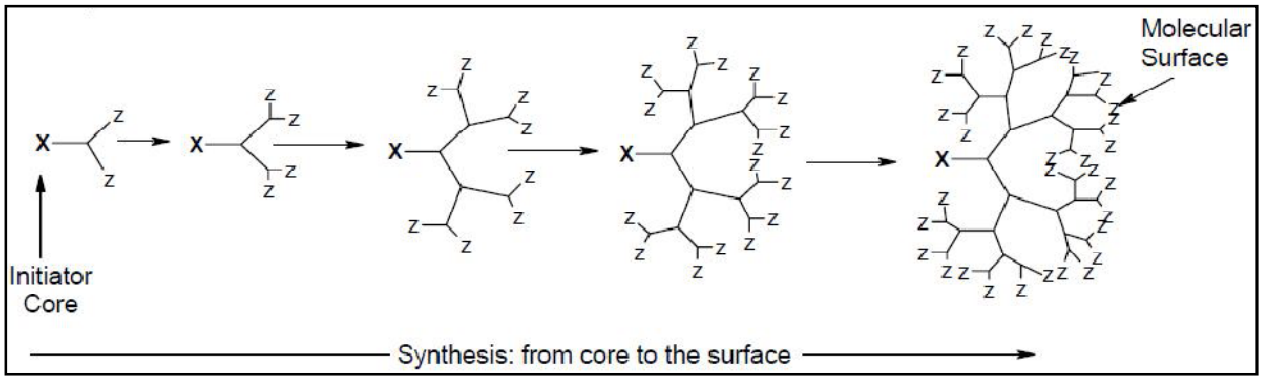

Figure 5: Divergent synthesis of dendrimer

Convergent synthesis

Convergent approach of dendrimer synthesis overcomes the purity and structural defect issues of divergent synthesis. By this approach more uniform and symmetric dendrimers can be synthesized but with lower overall yield. In other words yield is sacrificed for purity and this approach is generally used for laboratory scale dendrimer synthesis. For commercial scale production, divergent synthesis is still favored. Most commonly used commercially available dendrimers are PAMAM and PPI, which are structurally somewhat different in every batch due to structural defects. [16, 28]

Convergent approach of dendrimer synthesis was first introduced by Jean Frechet. In this approach dendrons that ends up to terminal groups are synthesized first and in final step these are linked together to a core molecule for getting complete dendrimer structure as shown in figure 4. Dendrimers synthesized by this way have less impurities, more monodispersity and symmetry because better purification is possible of dendrons before final attachment to core. But the size of dendrimer synthesized by convergent approach have limitation due to steric hindrance between dendrons going to attach with core. This size limitation is not with divergent approach of dendrimer synthesis. [14,29]

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 (figure 6). [22-24]

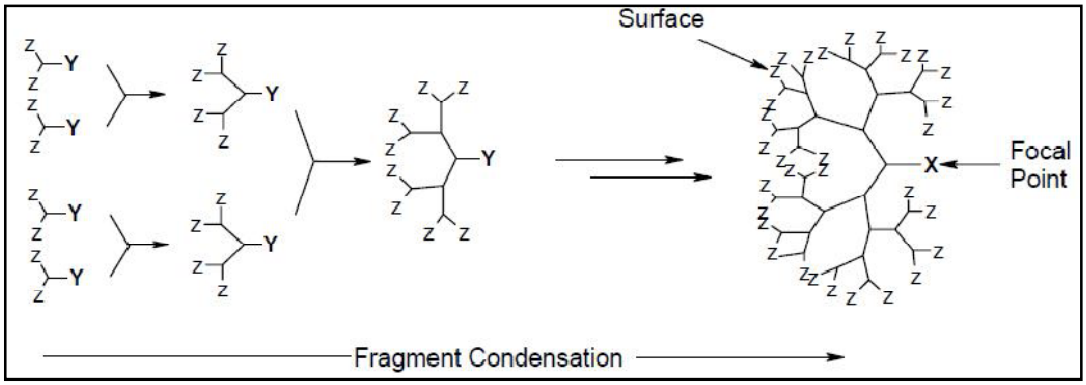

Figure 6: Convergent synthesis of dendrimer

Double Exponential and Mixed Method:

This is amixture of both divergent and convergent method. In this method a single starting material is taken from which two monomers are prepared by divergent and convergent method. Then these two monomers are reacted together to give an orthogonally protected trimer. This protecter trimer may be use to repeat the growth process again (figure 7).[7,16]

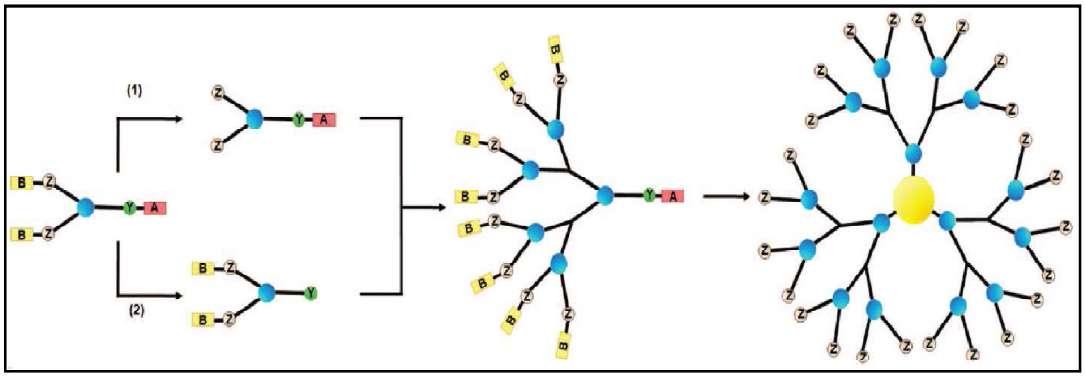

Figure 7: Double Exponential and Mixed Method

Advantages of Dendrimers in Comparison with other Polymers

The classical polymerization process, which results in linear polymers, is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis. Dendrimers are monodisperse macromolecules, unlike linear polymers. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological (it's property of the flow behavior) properties.[11-14]

Characteristic of Dendrimers

Architecture: Dendrimers shows improved physical and chemical properties due to their molecular architecture. The dendrimers shape depend on the generation i.e. lower generation shows open planar elliptical shape while higher generation shows compact-spherical shape. [17]

Solubility: Surface groups of the dendrimers plays an important role in the solubility of dendrimers. If the surface end groups are hydrophobic in nature, then dendrimers are soluble in nonpolar solvent. If the surface end groups are hydrophilic in nature and dendrimers are soluble in polar solvent. The high solubility, miscibility and reactivity and binding capacity of dendrimers is due to the presence of many chain end groups. [17-20]

Monodispersity: Dendrimers are monodisperse in nature i.e. they have isomolecular species, whose molecular size, shape and disposition of organic moieties are adjusted and controlled. [21]

Viscosity: In solution dendrimers form a tightly packed ball which influences its rheological properties. The intrinsic viscosity dendrimers solution does not exhibit linear relationship with mass but it is highest for a specific generation and then it begins to decrease.[6-9]

CHARACTERIZATION OF DENDRITIC POLYMERS [11, 18, 23]

- Spectroscopic techniques (UV-Visible, IR, NMR)
- Microscopy (*TEM* , *AFM, SEC)*
- Rheology, physical properties (DSC)
- Miscellaneous
- Scattering techniques
- Electrical techniques
- Solubility
- Determination of Melting Point
- Elemental Analysis (Nitrogen)

APPLICATIONS OF DENDRIMERS

When drug is conjugated with dendrimer , it increases its half-life. For example half-life of methotrexate is increased to 24 hours from 24 minutes when conjugated with dendrimer. This longer circulating half-life also increase its efficacy due longer contact time with target site. This also decrease the frequency of drug administration as well as increases patient compliance. Solubility of drug is found greatly enhanced when conjugated with dendrimer. For example paclitaxel solubility is enhanced by 9000 fold when conjugated with dendrimer.

Polyethylene glycol (PEG) attached between drug and dendrimer also plays an important role in enhancing solubility of drug. [6,30-32]

1. **Therapeutic Application:**
   - Dendrimer in photodynamic therapy
   - Dendrimers for Boron Neutron capture therapy
2. **Diagnostic Application:**
   - Dendrimers as MRI contrast agent
   - Dendrimers as X-Ray contrast agent
   - Dendrimer as molecular probe
3. **Pharmaceutical Application:**
   - Dendrimers in pulmonary drug delivery
   - Dendrimers in Transdermal drug delivery
   - Dendrimers in ocular drug delivery
   - Dendrimers in oral drug delivery
   - Dendrimers for controlled release drug delivery
   - Dendrimers in targeted drug delivery
   - Dendrimers in gene delivery
   - Dendrimers as solubility enhancer
   - Cellular delivery using Dendrimers carrier
   - Dendrimers based product in cosmetics
   - Dendrimers based commercial products
4. **Dendrimers in Gene Delivery**
5. **Dendrimers as Solubility Enhancer**
6. **Dendrimers as Cellular Drug Delivery CarrierDendrimers in Targeted and Controlled Release Drug Delivery**
7. **Dendrimers in Cosmetics**
8. **Dendrimers as a light harvesting antennae**

RECENT ADVANCEMENT OF DENDRIMER IN CANCER THERAPY [10,26-29]

Delivery vehicle for anticancer agents that are poorly soluble in water, a research team at Boston University and the Research Triangle Institute (RTI) has developed a biocompatible dendrimer that wraps itself around water-insoluble drugs. The investigators have used this dendrimer to create water-soluble formulations of three promising anticancer agents belonging to the camptothecin family, which also includes

the widely used drugs topotecan. Polyamidoamine (PAMAM) dendrimers has received muchattention for their ability to solubilize water- insoluble drugs and their ability to promote the transport of drugs across biomembranes. In one study an efficient transdermal drug delivery system (TDDS) consisting of a polyhydroxyalkanoate (PHA)-based system with a polyamidoamine dendrimer was examined for the transdermal delivery of tamsulosin. By adding the dendrimer, the dendrimer-containing PHA matrix achieved the clinically rerequired amount of tamsulosin permeating through the skin model

CONCLUSIONS

Review study on dendrimer for various synthetic strategies for dendrimer synthesis. In general dendrimers can be synthesized by two techniques that is divergent and convergent approach. In divergent approach, synthesis is started with a core molecule which grows outwards. In convergent approach, dendrons are synthesized first and then connected to the core molecule inward. Divergent approach is used for commercial scale production of dendrimers because by this approach good yield is obtained but purity is sacrificed. Various types of structural defects are possible in divergent synthesis of dendrimers like missing repeat unit, intramolecular and intermolecular cyclization, ester hydrolysis, retro Michael reaction etc. Convergent approach is used for laboratory scale production of dendrimers with higher purity and lesser defects but yield is sacrificed. Dendrimers synthesized from convergent approach are more uniform and symmetrical with lesser defects because purification can be done at dendron stage that is before attaching to core molecule. Dendrimers have various applications. In the field of pharmaceutical sciences these are specially used for enhancing half-life of drugs and reducing frequency of drug administration. Dendrimers are also used for enhancing solubilities of various drugs.

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