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Review Article

DENDRIMERS: AS PROMISING NANOCARRIERS FOR DRUG DELIVERY

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ABSTRACT

D*endrimers are a new class of synthetic polymers which have the structure like a tree or star shape, with a central core, interior branches and terminal groups which decorate the surface. Cavities inside the core and the interior branches can be modified to carry hydrophobic and hydrophilic drugs. The terminal groups on the surface can also be adapted to carry drugs or antibodies for neutralizing or targeting purposes. These artificial macromolecules may be synthesized to reach the size of nano objects having dimensions similar to proteins. Recently, dendrimers have successfully proved themselves as promising nanocarriers for drug delivery because they can render drug molecules a greater water-solubility, bioavailability, and biocompatibility. These features have made their application in pharmaceutical, nanotechnology and medicinal chemistry particularly attractive. This review focuses on properties and various applications of dendrimers.*

INTRODUCTION

A dendrimer is generally described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers have often been refered to as the "Polymers of the 21st century". Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers. He synthesized the first "cascade molecules". In 1985, Donald A. Tomalia synthesized the first family of dendrimer. The word "**dendrimer**" originated from two words, the Greek word dendron, meaning tree, and meros, meaning part. At the same time, Newkome's group independently reported synthesis of similar macromolecules. 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. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.

ADVANTAGES OF DENDRIMERS

1. Due to stringent control during synthesis, they have lower polydispersity index.
2. Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body.
3. Dendrimers can be modified as stimuli responsive to release drug.
4. Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectively than small molecules.
5. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.
6. High density and reactivity of functional groups on the periphery of dendrimers make multifarious bioactive molecules to be easily modified on to the surface.
7. Well defined globular structure, predictable molecule weight and monodispersity of dendrimers ensure reproductive pharmacokinetics.
8. Controllable size (generation –dependent) of dendrimers satisfies various biomedical purposes.
9. High penetration abilities of dendrimers through the cell membrane cause increased cellular uptake level of the drugs complexed or conjugated to them.

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Disadvantages of dendrimers:

1) The signal from dendrimer hybridization is rather punctate, and spot finding algorithms are less successful at defining the spots than it is with other types of probes.
2) The procedure takes longer than more standard techniques, because it involves two successive hybridizations

STRUCTURE OF DENDRIMER:

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. 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.

Dendrimers possess three distinguished architectural components namely

(i) An initiator core.
(ii) Interior layers (generations) composed of repeating units.
(iii) Exterior (terminal functionality) attached to the outermost interior generations.

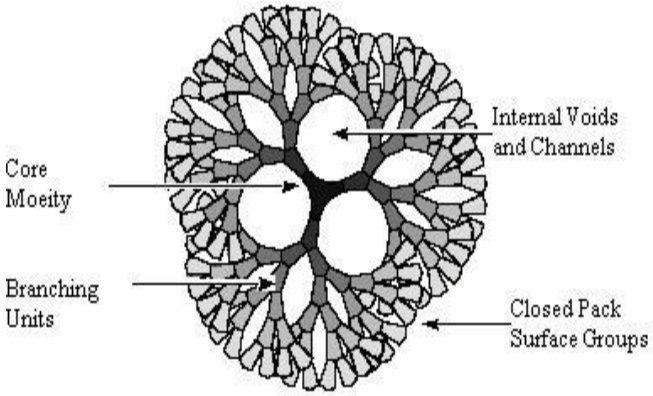

Figure 1: The Dendritic Structure

Components of a Dendrimer Structure

1. Generation

It is the hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural 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, e.g. a 5th generation polypropylene imine is abbreviated to a "G5-PPI-" dendrimer, The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented here "G0". The core structure thus presents no focal points, as hydrogen substituents are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted half-generations; a well-known example is the carboxylic acid-terminated PAMAM dendrimers.

2. 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.

3. 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).

4. 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".

DENDRIMER FAMILIES:

1. PAMAM Dendrimers

Poly (amidoamine) (PAMAM) dendrimers are the first synthesized and commercialized dendrimers family. Synthesis of PAMAM dendrimers is initiated using an alkyldiamine core (e.g., ethylene diamine; EDA), which reacts via Michael addition with methyl acrylate monomers to produce a branched intermediate that can be transformed to the smallest generation of PAMAM dendrimers with NH2, OH,or COOH surface groups. The reaction of this branched intermediate with excess EDA produces G0 with four NH2 surface groups. Similarly, the reaction of the same intermediate with ethanolamine produces G0 with four OH surface groups. Hydrolysis of the methyl ester in this intermediate produces the smallest anionic dendrimer (G0.) with four COOH groups. Synthesis of higher generations of PAMAM dendrimers is achieved by sequential Michael addition of methyl acrylate monomers followed by an exhaustive amidation reaction with EDA. This synthesis method produces highly organized and relatively monodisperse polymers that display a controlled incremental increase in size, molecular weight, and number of surface groups with the increase in generation number.

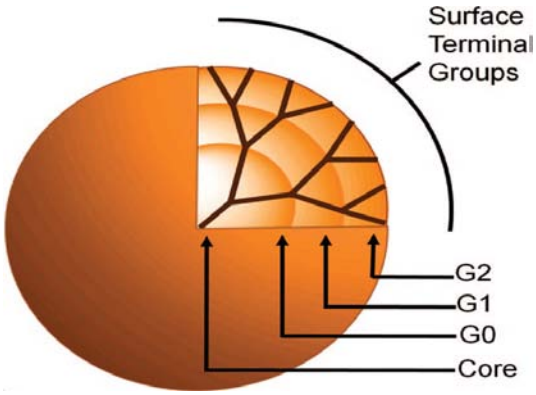

Figure 2: Schematic drawing of a G2 dendrimer

2. Biodegradable Dendrimers

The need for biodegradable dendrimers emerged as a strategy to produce the desired large molecular weight carriers that achieve high accumulation and retention in tumor tissue while allowing fast and safe elimination of dendrimer fragments into the urine to avoid nonspecific toxicity. Biodegradable dendrimers are commonly prepared by inclusion of ester groups in the polymer backbone, which will be chemically hydrolyzed and/or enzymatically cleaved by esterases in physiological solutions. Because of their biodegradability and biocompatibility, polyester dendrimers have been utilized for delivery of anticancer drugs.

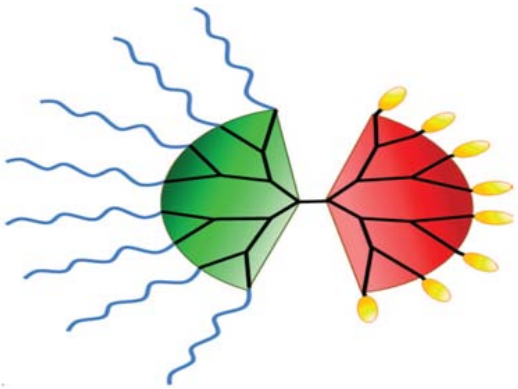

Figure 3: Dendrimer core

3. Amino Acid-Based Dendrimers

Amino acid-based dendrimers were developed to capitalize on the unique properties of the amino acid building blocks including chirality, hydrophilicity/hydrophobicity, biorecognition, and optical properties. For example, chirality of amino acid-based dendrimers is a product of the chirality of the core, branching units, and terminal surface groups, which influence the arrangement of the surface groups and the overall shape of the dendrimer.

Amino acid-based dendrimers are synthesized using one of the following strategies:

(1) Amino acid or peptide grafting and display on the surface of a conventional dendrimer or

(2) Attachment of amino acids or peptides to an organic or peptide core.

4. Glycodendrimers

Carbohydrate interactions with different receptors displayed at the cell surface control a number of normal (e.g., lymphocyte activation and cell-cell adhesion) and abnormal (e.g., cell-pathogen adhesion and cancer cell metastasis) biological processes. The affinity of carbohydrate-receptor interactions is typically low for a single carbohydrate ligand but has been shown to increase significantly through multivalent ligand-receptor interactions, which result in clustering and cross-linkage of the displayed receptors. .

5. Hydrophobic Dendrimers

Dendrimer-based drug delivery systems should be watersoluble to facilitate their systemic administration. However, the inclusion of hydrophobic regions in the dendrimer structure allows for better encapsulation and efficient solubilization of hydrophobic drug molecules within the dendrimer voids. Specifically, dendrimers with hydrophobic cores proved to effectively retain hydrophobic drug molecules in the voids of their branching architecture, mimicking amphiphilic polymer micelles. However, unlike polymeric micelles, which require a specific "critical micelle concentration" to remain intact in solution, dendrimers building units are covalently bound and do not dissociate in diluted solutions. .

6. Asymmetric Dendrimers

Asymmetric dendrimers are synthesized by coupling dendrons of different generations to a linear core, which yields a branched dendrimer with a nonuniform orthogonal architecture. This asymmetry allows for tunable structures and molecular weights, with precise control over the number of functional groups available on each dendron for attachment of drugs, imaging agents, and other therapeutic moieties.

SYNTHESIS OF DENDRIMERS:

1. Divergent Synthesis

Divergent dendrimer synthesis is a technique that effectively grows the dendrimer structure from the initiator core to the periphery in a stepwise fashion by iterative addition of monomer units. Specifically, divergent synthesis is initiated by coupling of a monomer unit to a multifunctional initiator core where the dendrimer generation increases by successive addition of the building blocks to the surface of the parent dendrimer Tomalia and co-workers used this strategy to couple *N*-(2-aminoethyl) acrylamide monomers to an ammonia core to develop PAMAM-NH2 dendrimers... PAMAM dendrimers are the first class of dendrimers that were systematically synthesized, characterized, and commercialized using the divergent synthesis.

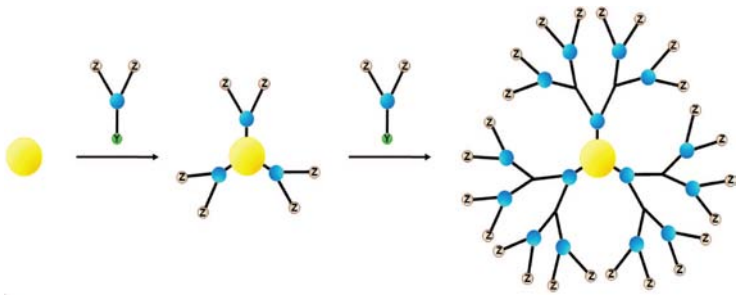

Figure 4: divergent method for synthesis of dendrimers

2. Convergent Synthesis

Convergent synthesis begins with the dendrimer surface units coupled to additional building blocks to form the branching structure, thus constructing dendrons from the periphery toward the central focal point .Each dendron is then coupled through its focal point to a multifunctional core to produce the complete dendrimer. Unlike divergent synthesis, convergent reactions are simple to purify since the desired dendrons are substantially different from the reaction byproducts, thus eliminating the need for highly efficient reactions. .

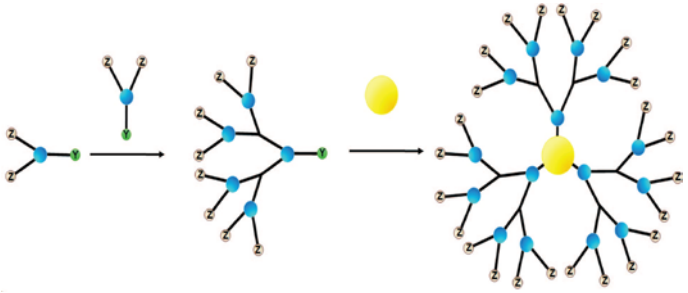

Figure 5: convergent method for synthesis of dendrimers.

3. Combined Convergent-Divergent Synthesis

A hybrid convergent-divergent synthesis called "double exponential growth" to further accelerate dendrimer synthesis by using orthogonally protected branched monomers with protecting groups that are stable during cleavage of the opposing functionality The approach begins with selective deprotection of the branched monomer surface groups to produce an activated convergent monomer or deprotection of the focal point resulting in a divergent monomer. Coupling of these products gave the first-generation dendrimer by the divergent approach. The parent dendron can then be exponentially grown by coupling to an activated dendron, where each additional activation and coupling sequence doubles the final dendron generation. The complete dendrimer can then be prepared by coupling of the activated dendrons to a central core.

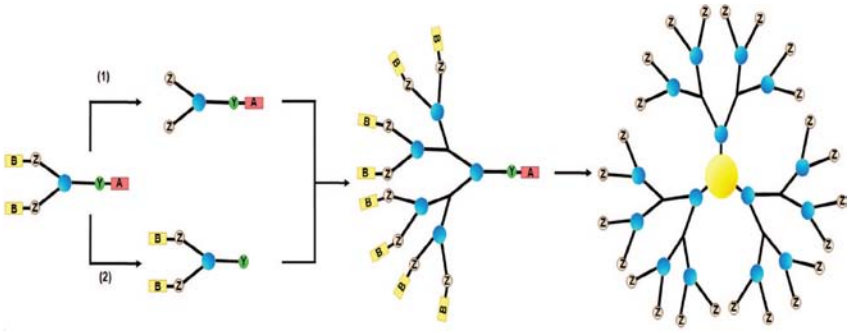

Figure 6: convergent-divergent method for dendrimer synthesis.

TYPES OF DENDRIMERS:

1. 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 (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 starlike pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

2. 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.

3. PPI Dendrimer

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

4 .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.

5. Multilingual Dendrimers

In these dendrimers, the surface contains multiple copies of a particular functional group.

6. Chiral Dendrimers

The chirality in these dendrimers are based upon the construction of a constitutionally different but chemically similar branches to chiral core.

7. Hybrid Dendrimers Linear Polymers

These are hybrids (block or graft polymers) of dendritic and linear polymers.

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

9. Micellar Dendrimers
These are unimolecular micelles of water soluble hyper branched polyphenylenes.

10. 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. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, e.g. vaccine and diagnostic research.

Effect of Various Factors on the Properties of Dendrimers

1. Effect Of pH
Amino-terminated PPI and PAMAM dendrimer have basic surface groups as well as a basic interior. For these types of dendrimers with interiors containing tertiary amines, the low pH region generally leads to extended conformations due to electrostatic repulsion between the positively charged ammonium groups, based on a highly ordered structure at low pH (pH<4).

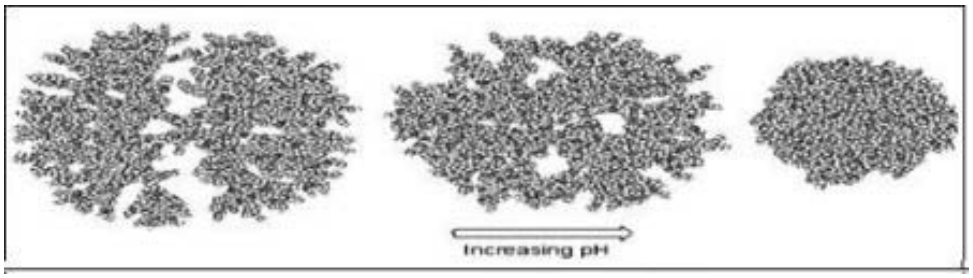

Figure 7:-PAMAM dendrimer, under different pH.

pH 2- the dendrimer core has the most extended conformation
pH 6- some degree of back-folding occurs
pH 11- the electrostatic repulsion between the negative charged forces.

2. Effect of Solvent
The ability of the solvent to solvate the dendrimer structure is a very important parameter when investigating the conformational state of a dendrimer. i.e. decreasing solvation. However, being more flexible, the low generation dendrimers show the highest tendency towards back-folding as a result of poor solvation compared to the higher generation dendrimers. whereas polar (good) solvents solvate the dendrimer arms Nonpolar aprotic (poor) solvents induce higher molecular densities in the core region as a result of back-folding,

3. Effect of Salt
High ionic strength (high concentration of salts) has a strong effect on charged PPI dendrimers and favours a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor salvation. At low salt conditions, the repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure.

Figure 8: conformational change of a PPI dendrimer upon increasing ionic strength

4. Effect of Concentration
PPI dendrimers (G4, G5) in a polar solvent like methanol show that the molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted.
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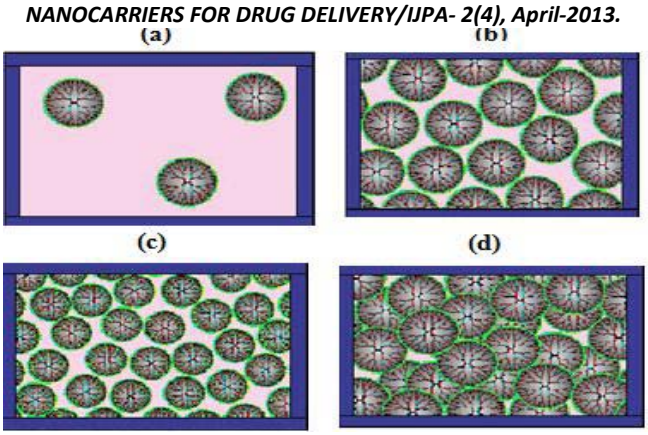

Figure 9: at different concentrations (a) Dilute (b) Contact (c) Collapse (d) Interpenetrate

METHODS FOR CHARACTERIZATION:

The earliest work on dendrimer characterization was concerned with aspects of the organic chemistry–did the proposed chemical reaction take place without side reactions and what was the conversion? Since near 100 % conversion and near perfect removal of excess reactants is required for making pure dendrimer, common methods of spectroscopy and chromatography can be used to verify the structure. In a wide variety of dendrimer chemistries, nearly perfect structures have been produced, at least for earlier generations where the techniques are more quantitative.

Table 1: Following methods can be used for characterization of dendritic polymers

S. NO		TECHNIQUES	APPLICATIONS
I		**SPECTROSCOPY TECHNIQUES NMR.**	Most widely used for dendrimers characterization. Analysis in step by step synthesis Of Dendrimer .To Probe The Size ,Morphology, Dynamics of Dendrimers for organic dendrimers such ad PPI,Polyphenylester.
	A	Special techniques of NMR 1H and 13 NMR Two dimensional: 1H, 1H COSY 1H,1H NOESY 1H,1H EXSY 1H,1H TOCSY	 For polyphenyacetylene or polyaryl dendrimers For PPI dendrimers For polyamide dendrimers For melamine dendrimers
	B	**UV-Vis method.**	Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units.
	C	**Infra red spectroscopy**	For routine analysis of the chemical transformations occurring at the surface of dendrimers.
	D	**Near infra red spectroscopy**	Used to characterized delocalize π-π stacking interaction between end group of modified PANAM.
	E	**Fluorescence**	The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers.
	F	**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.
	G	**X-ray diffraction**	This technique should allow precise determination of the chemical composition ,structure, size and shape of dendrimers
II		**MICROSCOPY** **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

IV		**ELECTRICAL TECHNIQUES**	Quantitative determination of the substitution
	A	**Electron paramagnetic resonance**	Efficiency on the surface of PANAM dendrimers. It
	B	**Electrochemistry**	give information about the possibility of interaction of electroactive end groups
	C	**Electrophoresis**	Used for the assessment of purify and homogeneity of several type of water soluble dendrimers.
V			
	A	**RHEOLOGY, PHYSICAL PROPERTIES** **Intrinsic viscosity**	Used as analytical probe of the morphological Structure of dendrimers.
	B	**Differential scanning calorimetry**	composition of polymers
	C	**Dielectric spectroscopy**	Used to detect the glass transition temperature which depends on thy moleculer weight, entangment and chain

APPLICATIONS

Applications of dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radioligands, imaging agents, or pharmaceutically active compounds. Dendrimers have very strong potential for these applications because their structure can lead to multivalent systems. In other words, one dendrimer molecule has hundreds of possible sites to couple to an active species. Researchers aimed to utilize the hydrophobic environments of the dendritic media to conduct photochemical reactions that generate the products that are synthetically challenged. .

1. A dendrimer: a polymeric macromolecule

Dendrimers are synthesized by a repetitive step-growth polymerization process. For example**, Starburst (Starpharma, Melbourne, Australia)** (PAMAM) dendrimers with a diaminobutane core are synthesized with alternating reaction with acrylic acid methyl ester and ethylenediamine This repetitive sequence of reaction steps theoretically allows the macromolecular dimensions of dendrimers to be controlled precisely. .

2. Cosmetics and personal care applications

Because of their excellent carrier properties, dendrimers have utility in cosmetics and personal care products such as hair-styling gels, shampoos, sunscreens, and anti-acne products.

3. Dendrimers as ophthalmic vehicles

PAMAM dendrimers were studied by Vandamme and Brobeck as ophthalmic vehicles for controlled delivery of **pilocarpine and tropicamide** to the eye.

4. Topical and transdermal delivery

Dendrimers have found recent applications in novel topical and transdermal delivery systems, providing benefits such as improved drug solubilization, controlled release, and drug-polymer conjugates (pro-drugs). .

5. Drug Delivery

Approaches for delivering unaltered natural products using polymeric carriers is of widespread interest, dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs.

6. Gene Delivery

PAMAM dendrimer/DNA complexes were used to encapsulate functional biodegradable polymer films for substratemediated gene delivery.

7. Sensors

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using poly(propylene imine), cadmium-sulfide/polypropylenimine.

9. Blood substitution

Dendrimers are also being investigated for use as blood substitutes. Their steric bulk surrounding a heme-mimetic centre significantly slows degradation compared to free heme\ and prevents the cytotoxicity exhibited by free heme.

10. Nanoparticles

Dendrimers also are used in the synthesis of monodisperse metallic nanoparticles. These nanoparticles range in width from 1.5 to 10 nanometers and are aptly called Dendrimer-Encapsulated Nanoparticles.

Table 2: Various dendrimer based products

PRODUCT	APPLCATION	COMPANY
Vivagel	Vaginal Gel for preventing HIV	Starpharma
Stratus CS	Cardiac Marker	Dade Behring
SuperFect	Gene Transfection	Qiagen
Alert ticket	Anthrax Detection	US Army Research Laboratory
Priofect, Priostar and STARBURST	targeted diagnostic, therapeutic delivery for cancer cells	starpharma

CONCLUSION

Dendrimer drug delivery systems are increasingly viewed as an advantageous solution for bioactive like drugs and gene. They provide a platform for the attachment of drugs or genes and their release through several mechanisms. Dendrimers can work as a useful tool for optimizing drug delivery of poor aqueous solubility such drugs. Although the application of dendrimers in the field of drug, gene, and vaccine delivery is in its infancy, dendrimers offer several attractive features, including the control one has over the primary nature of the system. They provide a platform for the attachment of drugs or genes and their release through several mechanisms. Boosting of commercial applications of dendrimer technology will provide strength for its usefulness in coming years.

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