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ReviewArticle

DENDRIMER: A NOVEL APPROACH FOR DRUG DELIVERY

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ABSTRACT

Dendrimers are 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. Dendrimers are macromolecules having highly branched, 3D structure, nanoscale architecture with monodispersity and high functionality. Dendrimers are dominated by the functional groups on the molecular surface for example; a dendrimer can be water soluble when its end groups like a carboxylic group. These features make it attractive candidates as drug carrier for controlled release or targeted delivery. Dendrimer is a smart polymer having various applicability in pharmaceutics, industry and diagnosis.

Key words: Dendrimer, PAMAM, Monodispersity, Polydispersity, Dendritic, PPI.

INTRODUCTION

Drug delivery is an important method of formulation that gives a choice of dosage form that enhances the bioavailability, enhances the solubility, targets the action and reduces the toxicity. One of the main approaches which are fulfilling the above criteria is Dendrimers. The word “dendrimer” originated from two words, the Greek word “Dendron”, meaning tree, and “meros”, meaning part. Dendrimers are different from the traditional polymer in that they have a multi-branched, three dimensional architecture with very low polydispersity and high functionality. Dendrimer is a type of nanoparticle based drug delivery system, which is macromolecule of highly symmetrical, hyper-branched, globular structure consisting of tree-like arms or branches. They have architecture of-

1. Core-determines the size and shape of the dendrimer
2. An interior of shells-determines the amount of the void space that can be enclosed by the dendrimer
3. An exterior layer- allows growth of the dendrimer or the chemical medication

This unique structure makes Dendrimersmonodisperse macromolecules as compare to classical linear polymer. In dendritic structures number of terminal group increases exponentially with a linear increase in the generation of dendrimer. This relationship is limits the ultimate size of the dendrimer due to steric crowding of the terminal groups.[1, 2, 3]

OBJECTIVES

1. Improve the pharmacokinetic and pharmacodynamics properties of a drug so that increase the bioavailability.
2. Achieve the controlled and targeted release of drug for the specific site of action.

STRUCTURE OF DENDRIMERS

Dendrimer formation is starts from an atom such as nitrogen and the carbon and other elements are attached by repeating series by chemical reactions to produce a spherical branching structure. The resulting dendrimers will have a similar size to albumin and hemoglobin, but smaller than multimers such as IgM antibody complex. Dendrimer possess three distinguished components namely-

1. An initiator multi functional core
2. Interior layers (generations) with repeated branching units, which are radically attach to the core.
3. Exterior surface functional group (terminal functionality) attached to the outer most interior layers.[4,5,6]

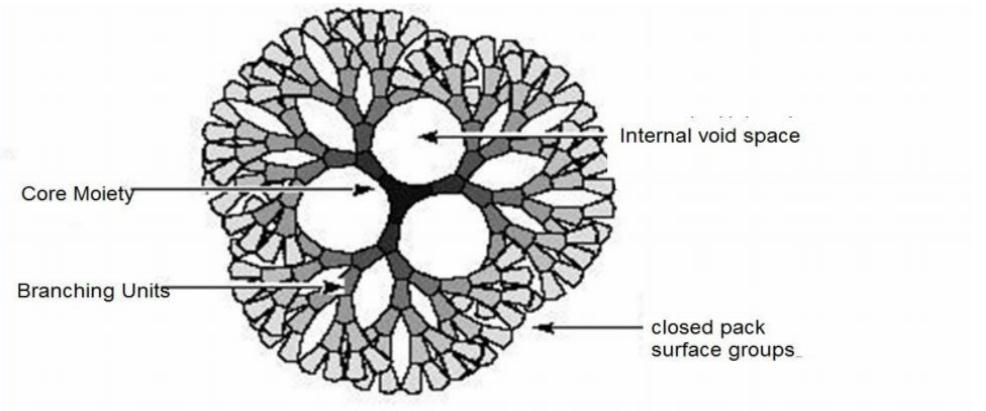

Figure 1: The dendritic structure [4]

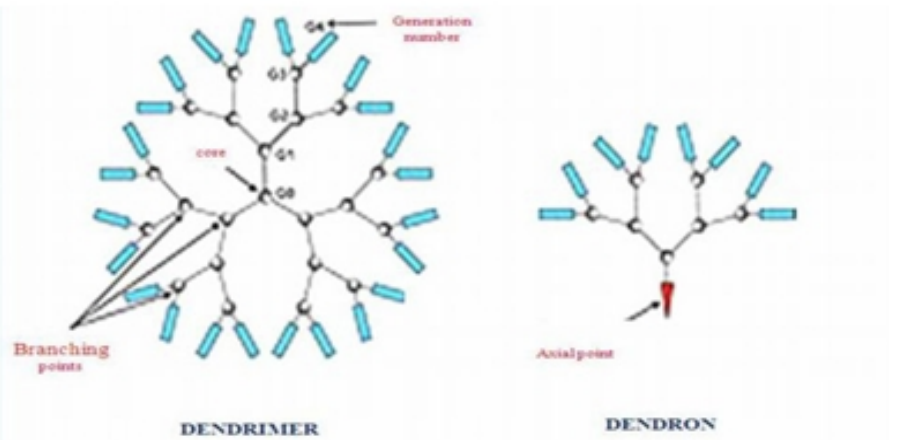

Figure 2: General structure of dendrimer and Dendrons [4]

COMPONENTS OF DENDRIMERS:[4]

Pincer-The outer shell of dendrimers contains a large number and deferent type of pincers formed by the last focal point headed before the dendrimer surface.
Due to the division in the chain of dendrimers at the focal points, the number of the surface groups present.

Shell-The dendrimer shell is the generation space (i.e. the homo-structural spatial segment) between the focal points. The space between the last outer branching point and the surfaceis the outer shell and the inner shell are generally known as the dendrimer interior.

Generation-It is a hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points). Generation numbers is the number of focal points present in the dendrimer and are counting from the core to the dendrimer surface i.e. a dendrimer having five focal points when moving from the center towards the periphery is signified as the 5th generation dendrimer and are written as G5-dendrimer.E.g.- A 5th generation polypropylene amine is also known as G5-PPI dendrimers. The core of the dendrimer is sometimes designated as generation zero (G0) i.e. the core structure have no focal points, as hydrogen substituent's are not considered as focal points. Intermediates formed during the dendrimer synthesis are sometimes termed as half-generations; for example the PAMAM dendrimers terminated with carboxylic acid.

End-Group-End group are generally known as the surface group of the dendrimer or terminal group. Dendrimers terminated with amine end-groups are named as amino-terminated dendrimers.

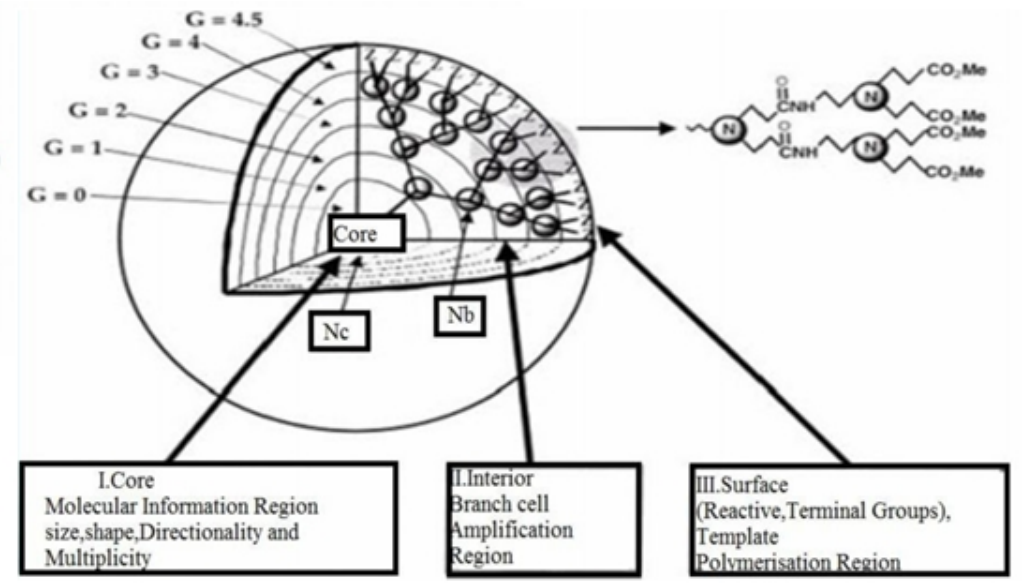

Figure 3: Three dimensional projection of dendrimer core-shell architecture for G is 4.5 PAMAM dendrimer with principle architectural components (1) core, (2) interior and (surface) [26]

PROPERTIES[7, 8, 9]

1. Dendritic polymers that can be made up of a well-defined molecular structure, i.e. being mono-disperse, unlike to linear polymers.
2. Nanoscale sizes that have similar dimensions to important bio-building blocks, e.g., proteins, DNA.
3. When dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) that show the non or low-immunogenicity.
4. The ability of drug excretion from body is a function of nanoscale diameter.
5. An interior void space is used to encapsulate small molecule of drugs, metals, or imaging moieties that reduces the drug toxicity and facilitates controlled release.
6. Numbers of terminal surface groups suitable for bioconjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.
7. Surfaces of dendrimers are designed with functional groups to resist trans-cellular, epithelial or vascular bio permeability.
8. Dendrimers are monodisperse macromolecules. Size and molecular mass of dendrimers can be controlled by polymerization proess.
9. When the molecular mass of dendrimers increases, then the intrinsic viscosity is increase at the fourth generation and then resulting begins to decline.
10. The presence of many chain-ends on the surface is responsible for the high solubility and miscibility and for high reactivity.
11. Dendrimer solubility is strongly depending on the attachment of nature of surface groups.
12. The dendrimer should be: nontoxic, on-immunogenic, able to cross bio barriers (biopermeable), able to stay in circulation for the time needed to have a clinical effect andable to target to specific structures.

TYPES OF DENDRIMER-[10]

1. PAMAM Dendrimer
2. PPI Dendrimer
3. Chiral Dendrimer
4. Multilingual Dendrimer
5. Tecto Dendrimer
6. Hybrid Dendrimer
7. Amphiphilic Dendrimer
8. Frechet-type Dendrimer
9. Peptide Dendrimer
10. PAMAMOS Dendrimer

PAMAM Dendrimer [poly (amido amine)]: PAMAM dendrimers are spheroidal or ellipsoidal in shape. These are most studied macromolecules and are commercially available. The deferent method is used for the synthesis. Where ammonia or ethylenediamine is used as a starting material. The high solubility and reactivity of dendrimer is depending on the presence of a number of functional end groups and empty internal cavities. The density of amino group is low in conventional macromolecules as compared to PANAM dendrimers.[10, 11, 12, 13]

PPI/POPAM Dendrimer: PPI means poly (propyleneImine)/poly (propylene amine).It's core structureis based on Diamino butane with primary amines as end groups and tertiary-propylene amines as interior. These are commercially available and also known as G-5 and are widely used in material science and biology.[10,14,22]

Chiral Dendrimer: The chirality of the dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core.[10,22]

Multilingual dendrimer: These are the dendrimers which contain multiple copies of a particular functional group on their surface.[15,10]

Tecto dendrimer: 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.[22,10]

Hybrid Dendrimer: These dendrimers have characters of both dendritic and linear polymer.[10, 22]

Amphophillic Dendrimer: These are containing both group, one half that is electron donating and another half is electron withdrawing.[32, 22]

Peptide Dendrimers: Peptide dendrimers are those which contain amino acid as branching or interior unit. These are used for diagnostic purpose and vaccine delivery.[16, 10]

Ferchet-type Dendrimer: These are based on polybenzile ether hyper branched skeleton. Carboxylic acid group found upon the surface of dendrimer which provides site for further fictionalizations and also enhance the solubility of dendrimers.[16, 22]

PAMAMOS dendrimers [poly (Amidoamineorganosilicon)]: These are silicon containing first commercial dendrimers. These are inverted unimolecular micelles that contain exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophillic polyamidoamines.[10, 16, 32]

SYNTHESIS OF DENDRIMERS-

1. Divergent growth method
2. Convergent growth method
3. Hyper cores and branched monomers growth
4. Double exponential growth

Divergent growth method: This method was introduced by *Tomalia*. In this method growth of dendrimers originates from a core site. The core is react with two or more moles of reagent containing atleast two protecting groups, lead to the first generation dendrimers. This process is further repeated until the dendrimer of the described size is obtained. By this approach the first synthesized dendrimers were polyamidoamines (PAMAM), also known as starbust dendrimers.[1, 20]

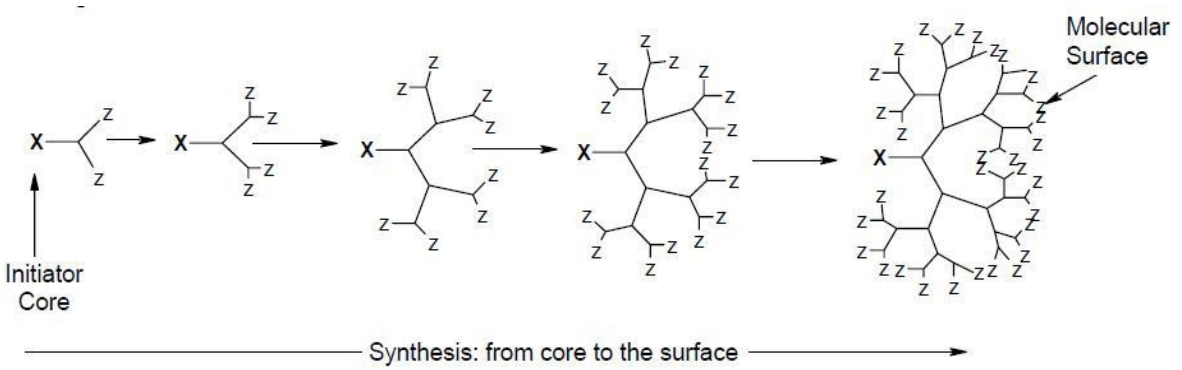

Figure 4: Divergent growth method [20]

Convergent dendrimer growth: Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attach to a suitable core to give a complete dendrimer. Convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure in minimized, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the Dendrons and the core molecules.[1, 21, 17, 18]

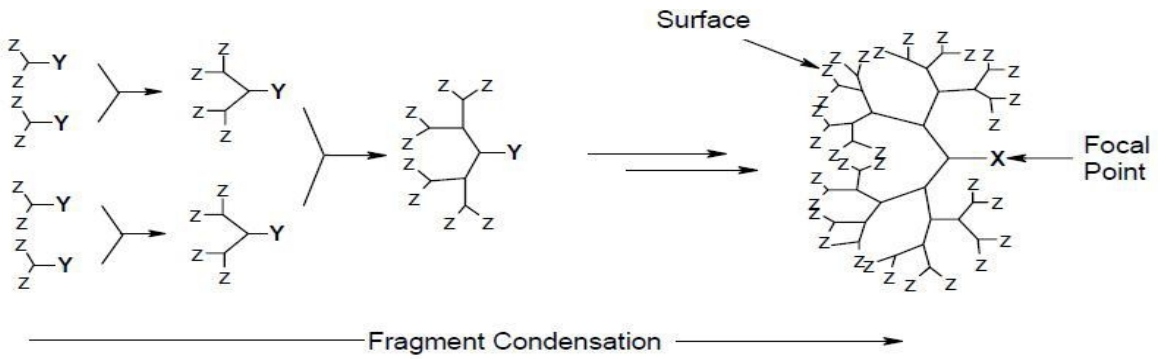

Figure 5: Convergent growth method[1]

Hyper cores and branched monomers growth: Connection of the oligomeric species in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing atleast two protecting branching site, followed by removal of the protecting groups. The successive liberated reactive sites lead to the first creation dendrimers.[1, 19]

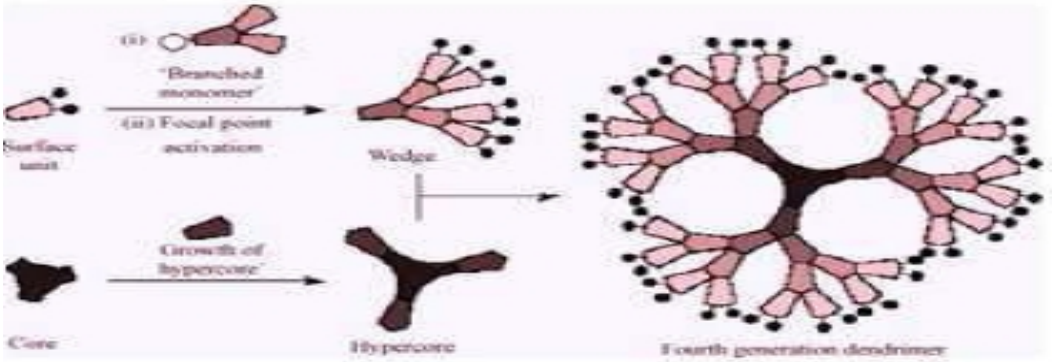

Figure 6: Hyper cores and branched monomers growth[19]

Double exponential or mixed growth: In this approach two products (monomers for convergent and divergent growth) are reacted together to give an orthogonally secluded trimmer, which may be used to repeat the growth process again, strength of double exponential growth is more slight than the ability to build large dendrimers in comparatively few steps.[1,20,21]

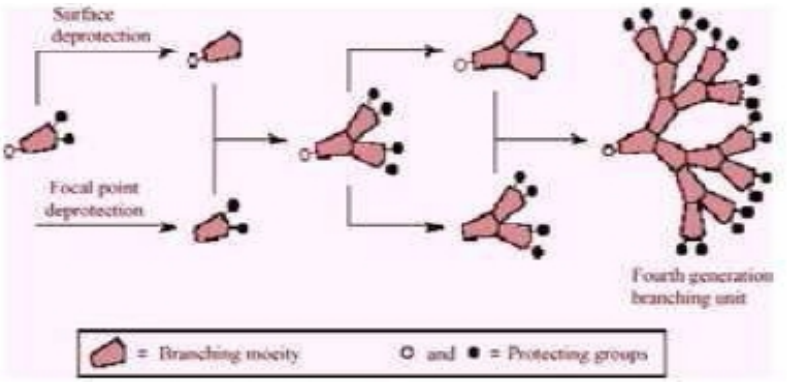

Figure 7: Double exponential or mixed growth[1]

ADVANTAGES OF DENDRIMERS

1. Dendrimer show a structural equivalence and monodispersity.
2. Dendrimers have a better/greater targeting good organization due to the presence of reactive functional groups on the surface of dendrimer. Terminal groups may also be modified to rearrange specific receptors.
3. 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, appreciation, and high affinity to antigen.
4. Dendrimers have the ability to deliver drug inside the cell or they may develop intracellular trafficking.
5. Dendrimers have a capability to capture a variety of drug having different types of functional groups in internal hollow core or by charge interactions.
6. Dendrimers can be made stimuli responsive.
7. Dendrimers have limited toxicity and immunogenicity but good biodegradability.
8. They have better colloidal, biological and shelf-stability.
9. They may be intrinsically anticancer agents in nature due to interferon, tumour necrosis factor including properties of acrylates.[22, 23, 24, 25]

FACTOR AFFECTING DENDRIMERS SYNTHESIS

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

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

Some dendrimer defects events (e.g. dendrimer fragmentation) can influence the degree of monodispersity for the duration of dendrimer growth. This is especially true if fragments posses amine functions which may participate with the transmission sequencing agent to produce new but "regressed dendrimer" entities. They are usually due to following reasons:

1. Incomplete removal of reactant at each of generation sequences leads to polydispersity sine residual reactant function as an originator core to produce 0.5 generation and subsequent lower generations.
2. Exposure of dendrimers to higher temperature causes cyclization of dendrimers by intermolecular reactions.
3. The incomplete amount of sequencing agent may cause bridging of dendrimer or nonideal dendrimer formation.[22, 24]

FACTOR AFFECTING DENDRIMER PROPERTIES

Effect Of pH: The study of structural behavior of PAMAM dendrimers as a function of pH, by apply molecular dynamics show that the dendrimer has an complete conformation based on highly ordered structure at low pH (pH<4). At this pH, the interior is getting gradually more "hollow" as the generation number increases as a result of repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior. At neutral pH, back-folding occur which may be a consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. At higher pH the dendrimer contract as the charge of the molecule neutral, acquiring a more spherical structure, where the repulsive forces between the dendrimer arms and between the surface groups reaches the minimum. At this pH, the conformation has a higher degree of back-folding as a consequence of the weak "inter-dendron" repulsive forces.[26, 27, 28]

Effect Of Solvent: Dendrimers of all generation generally exhibit a large extent of back-folding with decreasing solvent properties, i.e. decreasing salvation. However, being more flexible, the low generation dendrimers show the highest tendency towards back-folding as aresult of poor salvation compare to the higher invention dendrimers.[26, 29]

Effect Of Salt: High ionic strength (high conc. Of salt) has a strong effect on charged PPI dendrimers 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 result in anextended conformation in order to minimize charge repulsion in the structure.[26,27]

Effect of Concentration: Small angle X- ray scattering experiments performed on PPI dendrimer (G4, G5) in a polar solvent like methanol demonstrate that the molecular conformation of dendrimer upon increasing concentration becomes gradually more contracted. This molecular contraction may minimize the repulsive forces between the dendrimers molecule and increase the ability of the dendrimers to demonstrate a more tight intermolecular packing.[26]

MECHANISM OF DRUG DELIVERY THROUGH DENDRIMERS

The well-defined 3D structure and various functional surface groups, drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers can function as drug carrier either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bond (prodrug)

There are broadly two mechanisms for drug delivery.

Drug molecules can be physically entrapped within the dendritic structure.

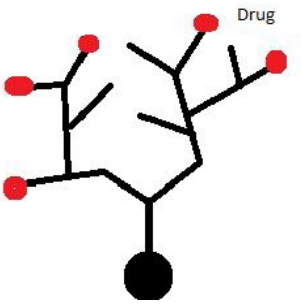

Figure 8: A dendrimer molecule with drug molecules loaded at terminal surface of branches

Drug molecules can be covalently linked onto the dendrimer surface (or) other functionalities to generate dendrimer-drug conjugate.[1,20,30,31]

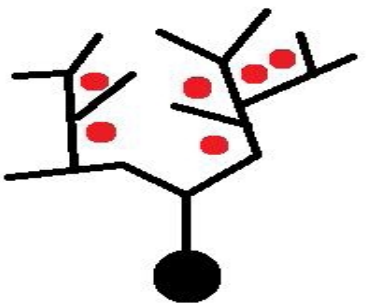

Figure 9: Dendrimer molecules with drug molecules encapsulated within branches

CHARACTERIZATION OF DENDRIMER BY VARIOUS METHODS

Spectroscopy and spectrometry method: Most widely used for dendrimers characterization like.[32,33,34]

Ultra-violet-visible spectroscopy: Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the no. of chromophoric units.

Infra red spectroscopy: For routine analysis of the chemical transformation occurring at the surface of dendrimers.

Near infra red spectroscopy: Used to characterize delocalize pie-pie stacking interaction between end group of modified PANAM.

Raman spectroscopy: Gave relevant information about the degree of cyclodehydrogenation of polyphenyl dendrimers, and the characterization of PPI and dendrimers.

Mass spectroscopy: Chemical ionization or fast atom phosphorus bombardment can be used only for the characterization of small dendrimers whose mass is below 3000 dalton. Eletrospray ionization can be used for dendrimers able to form stable multicharged species.

X-ray diffraction: This technique should allow precise determination of the chemical composition, structure, size and shape of dendrimer.

Nuclear magnetic resonance (NMR): Analysis in step by step synthesis of demdrimer. To probe the size, morphology and dynamics of dendrimers such as PPI etc.

Fluorescence: The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers.

Scattering technique[32,35,36]

Small angle X-ray scattering: 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.

Laser light scattering: To determine the hydrodynamic radius of dendrimers. Dynamic LLS is mainly used for detection of aggregates.

Small angle neutron scattering: Give access tothe 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 experiment conducted with PAMAM dendrimers and PPI dendrimers having labeled or unlabelled end groups

Microscopy methods[32,37,38]

Transmission microscopy: Electron or light produce image 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. E.g. atomic force microscopy.

1) **Size exclusive chromatography:** Allows the partition of molecules according to size.[32,39]
2) **Electrical technique**[32,40,41,42]

Electron paramagnetic resonance: Quantitative determination of the substitution efficiency on the surface of PANAM dendrimer.

Electrophoresis: Used for the assessment of purify and homogeneity of several type of water soluble dendrimer.

Electrochemistry: Gives information about the possibility of interaction of electroactive end groups.

Rheology and physical properties[32,43,44]

Differential scanning colarimetry: Used to detect the glass transition temperature which depends on the molecular weight, entanglement and chain composition of polymers.

Dielectric spectroscopy: Gives information about molecular dynamic processer.

Intrinsic viscosity: Used as analytical probe of the morphology structure of dendrimer.

Miscellaneous[32,45,46]

X-ray photo electron spectroscopy: Chemical composition of dendrimers such as poly Dendrons or PMMH dendrimers has been also obtained using XPS, even if this technique is most generally used for the characterization of layers.

Titrimetry: To determine the number of NH2 end groups of PAMAM dendrimers.

Sedimentation: For lactosylated PAMAM dendrimers, measurement of dipole movement for PMMH dendrimer.

APPLIATION OF DENDRIMERS

Pharmaceutical application

Dendrimer in ocular drug delivery: PAMAM dendrimers with carboxylic or hydroxyl surface groups, improving residence time and enhance bioavailability of pilocarpine in the eye.[47, 48, 49]

Dendrimer in pulmonary drug delivery: Positively charged PAMAM dendrimers increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.[47, 50]

Dendrimer in transdermal drug delivery: Dendrimers designed to be highly water soluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulation and to deliver drug efficiently.[7,53,54]

Dendrimer in oral drug delivery: Oral drug delivery studies using the human colon adenocarcinoma cell line, Caco-2, have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorption endocytosis.[7,51,55,56]

Dendrimer in targeted drug delivery: One of the effective cell specific targeting agents delivered by dendrimers is folic acid and methotrexate. DNA assembled dendrimer conjugates may allow the combination of different drug with different targeting and imaging agents so it is easy to develop combination therapeutics.[7, 52, 57]

Dendrimer for controlled release drug delivery: PEG chains and PAMAM dendrimers are used to deliver the anticancer drug 5-fluorouracil.[7]

Dendrimer in gene delivery: Dendrimer-based transfection agents have become routine tools for many molecular and cell biologists, dendrimers are extensively used as non-viral vector for gene delivery.[7, 53]

Dendrimer as solubility enhancer: Dendrimer have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular Micellar nature. They form covalent as well as noncovalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behavior.[7]

Therapeutic application

Dendrimers in photodynamic therapy (PDT): The photo sensitizer 5-aminolevunalic acid has been attached to the surface of dendrimer and studies as an agent for PDT of tumorigenic keratinocytes. This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue.[7, 47, 59,60]

Dendrimer for boron neutron capture therapy (BNCT): The radiation energy generated from the capture reaction of low energy thermal neutrons by 10B atoms has been used successfully for the selective destruction of tissue.[52,53]

Diagnostic application[61, 62, 63,64]

Dendrimers as molecular probes: The immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular prpbe, because of their large surface area and high density of surface functionalities.

Dendrimers as X-ray contrast agents: Number of potential dendritic X-ray contrast agents using various organometallic complexes such as bismuth and tin.

Dendrimers as MRI contrast agents: To improve the pharmacokinetic properties of dendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast agents have been considered.

Recent advancement of dendrimer therapy of cancer[65]

The Research Triangle Institute has developed a dendrimer that wraps itself around water insoluble drugs**.** This dendrimer have used to create water soluble formulation of three promising anticancer agents of camptothecin family, which also include the widely used drug topotecan**.**

MARKETED AVAILABLE DENDRIMERIC PRODUCTS-[7]

PRODUCT	APPLICATION	COMPANY
Vivagel	Vaginal Gel for preventing HIV	Starpharma
Stratus CS	Cardiac Marker	Dade Behring
Super Fect	Gene Transfection	Qiagen
Alert ticket	Anthrax Detection	US Army Research Laboratory

CONCLUSION

Dendrimers provide a platform for the attachment of drugs or genes and their release through several mechanisms which make them hopeful candidates for a lot of applications. Various applications of dendrimers have been explored during last three decades. A new era of research in dendrimers is the development of dendrimer cluster where several dendrimers are bound together to form a multifunctional therapeutic system, which will open new path for combination therapy which seems to be beneficial for treating diseases like cancer. This review clearly illustrates the different aspects of dendrimers as novel drug delivery system with the advent of more and more dendrimers used for it.

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