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Dendrimer: A Novel Drug Delivery System

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Abstract

Different types of novel drug delivery systems have developed comprising of various routes of administration, to attain controlled and targeted drug delivery, Dendrimers being one of them. Dendrimers are among the latest generations of nanosystems that constitute potential drug carriers. Dendrimer chemistry is one of the most captivating and rapidly growing areas of modern chemistry. In recent years Dendrimers have received significant consideration as drug delivery carrier. Dendrimer as a drug delivery agent is a promising, safe and selective drug delivery option. The most essential property of dendrimer is its highly selective nature for targeting the desired tissue that holds a promising future for the treatment of several disorders. Their safe, nontoxic and biocompatible nature makes them appropriate for site specific as well as prolonged drug delivery carriers.

Keywords

Dendrimers, Dendrimer chemistry, PAMAM, PPI, Nanoparticle, Novel drug delivery system, Targeted drug delivery.

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INTRODUCTION

The word "dendrimer" originated from two Greek words; i) Dendron: meaning tree, and ii) Meros: meaning part or segment. Dendrimer is a nanoparticle (10^{-9}). It is a branched macromolecule having a high degree of molecular uniformity, narrow molecular weight, distribution, specific size and shape characteristics and a highly-functionalized, terminal surface. [1, 2, 3] Due to its small size and easy uptake by cells, it has many advantages over other micro particles. These molecules act as vehicles for targeted drug delivery and controlled-release purposes as they can form covalent or non-covalent complexes with pharmaceutical compounds.

2. Goals:

(a) Enhance the pharmacokinetic and pharmacodynamics properties of a drug so that there is also an improvement in bioavailability.
(b) Achieve the controlled and targeted release of drug restricted to the desired area.

Developments observed in dendrimer patenting include synthesis, commodity, pharmaceutical, biotechnological, analytical and catalytic applications. Characteristic features of both molecular chemistry and polymer chemistry are exhibited by dendrimers. Dendrimers show opportunities for many applications in the fields of chemistry, biology and medicine especially in applications like drug delivery, gene therapy and chemotherapy. Dendrimers are also referred to as the polymers of 21st century. [2]

3. History:

- In 1978, Vögtle and his coworkers synthesized the first "Cascade Molecules". The first successful attempt. They saw the perspectives in using these polymers as molecular containers for smaller molecules.[4]
- In 1985, Donald A. Tomalia and his coworkers synthesized the first family of "Dendrimers" at Dow Chemicals.[5]
- In 1988, J.P. Tam created macromolecular dendritic peptide structures commonly referred to as ''Multiple Antigen Peptide''.[6]
- Newkome's group independently reported synthesis of similar macromolecules and called them "Arboroles".[6]

4. Structure of Dendrimers:

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 (Figure 1). As the process repeats, successive layers are added and the sphere can be expanded to the desired size. [7, 8]

Dendrimers possess three separate architectural components:

i) An Initiator Core:

Forms heart of the dendrimer molecules as all branches originate from this core. [8, 9]

ii) Interior Layers (Branching Unit):

Composed of repeating units, radically attached to the interior core. [8, 9]

iii) Exterior (Terminal Functional Groups):

Attached to the outermost interior generations. [8, 9]

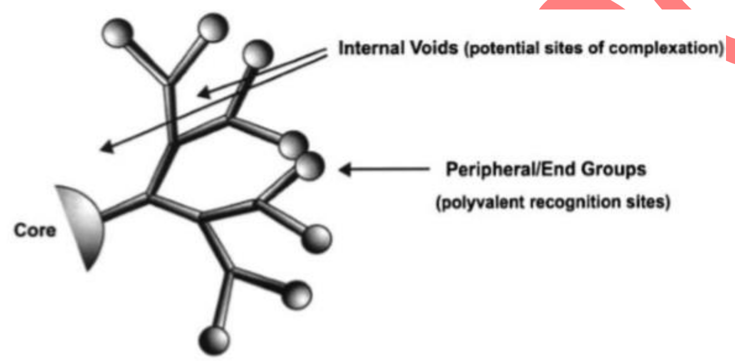


Figure 1: Schematic representation of dendrimer.

Dendritic copolymers are a specific group of dendrimers. There are two different types of copolymers:

a. Segment-block Dendrimers:

These dendrimers are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one polyfunctional core molecule. [10]

b. Layer-block Dendrimers:

They consist of concentric spheres of differing chemistry. They are the result of placing concentric layers around the central core. [10]

5. Properties of dendrimer:

i. Monodispersity:

The monodispersion means that the dendrimer has a well-defined molecular structure without any large individual variations. They are homogeneous due to their controlled synthesis and purification processes. [11, 12]

ii.Polyvalency:

The polyvalency is related to the quantity of reactive sites on outside of the dendrimer which are able to form connections with various materials of interest. [12, 14]

iii.Size and Shape:

The diameter of dendrimer increases as the generation increases. The size of the PAMAM G1 dendrimer was found to be around 1.1 nm whereas a G10 dendrimer had a size of about 12.4 nm. Lower generation dendrimers have ellipsoidal shape and higher generation dendrimers have spherical shape. [13, 15]

iv.Adaptive nature of dendrimers:

Depending on the polarity, ionic strength and pH of the solvent, dendrimers can adapt "native" (e.g. tighter) or "denatured" (e.g. extended) conformations.

v.Solubility:

Dendrimers generally have greater solubility in common solvents as compared to linear polymers. The solubility depends on various components like peripheral functional groups, nature of repeating units and even on the core. The dendrimer with hydrophilic end group is soluble in water whereas a dendrimer with hydrophobic end group is soluble in non-aqueous solvents. [16]

vi. Cytotoxicity:

Dendrimer cytotoxicity depends upon the central core but is also greatly affected by the peripheral groups on its surface.

vii. Back folding:

In the absence of solvent dendrons fold into the interior of the dendrimer towards the core known as back folding. This process is dependent on the ionic strength of the solvent. [17]

viii. Light harvesting property:

Dendrimers possess light harvesting property due to their tree-like structure that could potentially act as an energy gradient for the process of funneling. [18]

6. Advantages of dendrimers:

i. Delivery of medication to the affected part inside a patient's body directly.[2,19]
ii. Dendrimers are suitable for targeting solid tumors due to increased permeability, limited drainage in tumor vasculature.[2]
iii. Controlled and sustained release of drugs can also be obtained.[2]
iv. Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation.[2]
v. Dendrimers can be customized as stimuli responsive to release drug.
vi. Increase in therapeutic efficacy and decrease in side effects.[2,20]
vii. Relatively high drug loading.[2]
viii. Preservation of drug activity: As drugs can be incorporated into the systems without any chemical reaction.[2]
ix. Bypassing the gastric medium and hence avoiding the variation due to effect of gastric secretions.[2]
x. Overcoming the limitations of other nanoparticles for example: overcoming limitations of liposomes like:[2]
   a. Low encapsulation efficiency
   b. Rapid leakage of water-soluble drug in presence of blood components
   c. Poor storage stability

7. Types of Dendrimers:

S. No.	Types of dendrimer	Synthesis	Examples	Identification
1.	PAMAM (Polyamido mine) dendrimer	Divergent	Dendritech ™ (USA)	The PAMAM dendrimer has an interior core of ammonia or ethylenediamine.[21] A star like pattern is observed when looking at the structure of the high generation in two-dimensions. The generation levels of a PAMAM dendrimer range from 1 to 10 having a diameter in the range of 1.5nm to 14.5nm.[22] PAMAM dendrimers are widely used to solubilize insoluble drug molecules such as nifedipine and NSAID's like flurbuprofen by researchers all over the world.[23]
2.	PPI (Poly Propylene Imine) Dendrimer	Divergent	Asramol by DSM (Netherlands)	PPI dendrimers generally having numerous tertiary tris-propylene amines present in interior core and poly-alkyl amines as terminal functional groups. PPI dendrimers have attractive nano-characteristics for the delivery of nucleic acid and various biomedical applications.
3.	Chiral Dendrimer	Convergent [24]	Chiral dendrimers derived from Pentaerythritol	The chirality in these dendrimers is based upon the construction of constitutionally different but

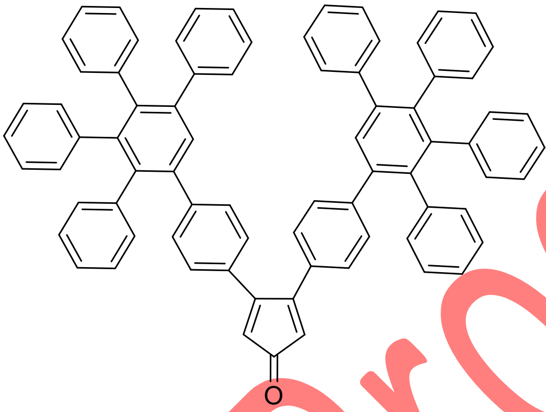
S. No.	Types of dendrimer	Synthesis	Examples	Identification
				chemically similar branches to chiral core. They are used as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.
4.	Multilingual Dendrimers	Convergent	VivaGel	These are the dendrimers which contain multiple copies of a particular functional group on their surface.[7]
5.	Tecto Dendrimers	Divergent	Stratus® CS Acute Care ™, Starburst®, Mercapto	Tecto Dendrimer is composed of a core dendrimer, which may or may not contain the therapeutic agent, surrounded by dendrimers.[7] These almost resemble the traditional PAMAM dendrimers and show similar properties. They perform varied functions ranging from diagnosis of disease state drug delivery, diseased cell recognition, reporting location to reporting outcomes of therapy.
6.	Hybrid Dendrimers	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes	Hybrid dendrimers are hybrids of dendritic and linear polymers in hybrid block or graft co- polymer forms; therefore they have characteristics of both dendritic and linear polymers.[7] They are obtained by complete mono functionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer.
7.	Amphiphilic Dendrimers	Divergent	SuperFect, Hydraamphiphiles and bola-amphiphiles	These dendrimers are built with two segregated sites of chain end, one half is electron withdrawing and the other half is electron donating.
8.	Frechet-Type Dendrimers	Convergent	Frechet type dendron azides, TM Priostar	These type of dendrimers have carboxylic acid groups as surface groups which serves 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.[25]
9.	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergent	SARSOX	These dendrimers are inverted unimolecular micelles that consist of hydrophilic and nucleophilic polyamidoamine interior cores with hydrophobic organosilicon terminal functional groups.[26] These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

S. No.	Types of dendrimer	Synthesis	Examples	Identification
10.	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	Vaccine and diagnostic research	It is a dendron-like molecular construct based upon a polylysine skeleton.

8. Classification of Dendrimers:

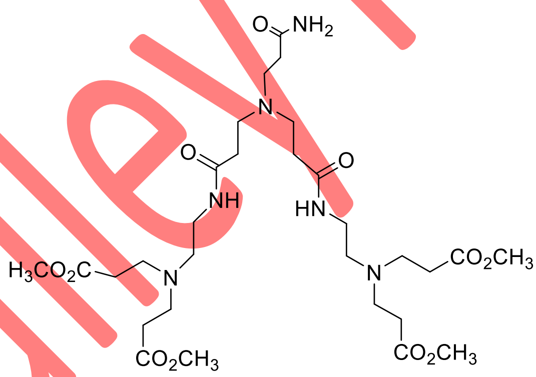
A. On the basis of Branching:

I. Phenyl branching:[27, 28]



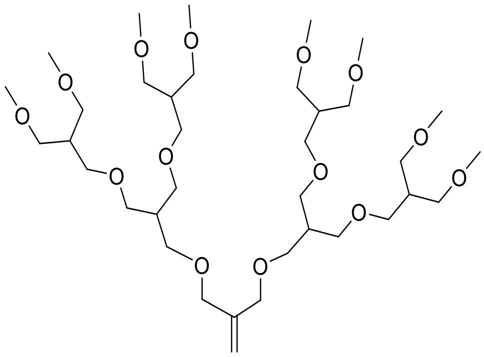
Poly (phenylene) branching

II. Amine branching: [29]



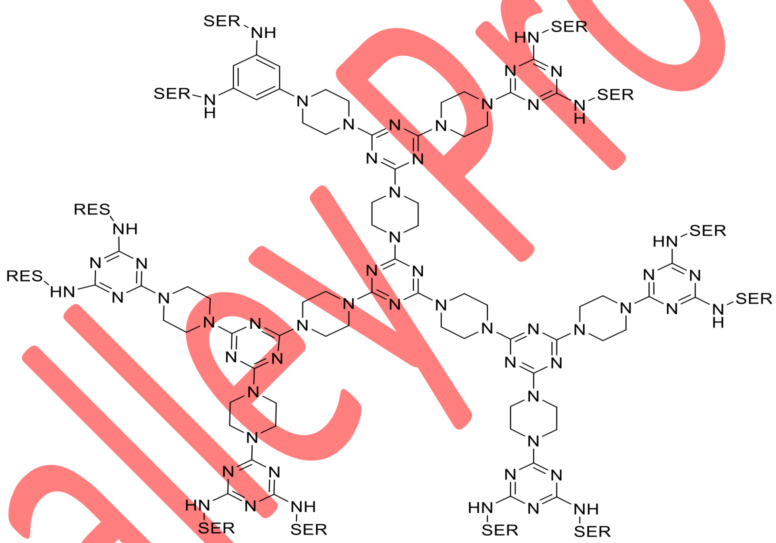
Amine branching

III. Alkyl branching: [30]



Poly (alkyl ether) branching

IV. Heterocyclic branching: [31]



Triazine branching

B. On the basis of Chemical Moieties and types of linkages in their structure:

I. Glycodendrimers:

Glycodendrimer is a general term used to describe a wide architectural range. These are those dendrimer that incorporate carbohydrate into their structure. [32]Depending on the position of the carbohydrate moiety in the structure, they are classified into:-

(a) Carbohydrate coated: These dendrimers contain the carbohydrate moiety at the periphery.

(b) Carbohydrate centered: These are the dendrimers contain a carbohydrate moiety as a core.[33]

(c) Carbohydrate based: These types of dendrimers consist solely of carbohydrate moieties. [33]

II. Peptide Dendrimers:

Peptide dendrimers are those dendrimers which hold amino acid as branching or interior core and having peptide on the surface of the traditional dendrimer framework. It is synthesized by the divergent method. They are used as drug delivery, contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and sero diagnosis. [25]

Peptide dendrimers can be divided into three types:

(a) Dendrimers with trifunctional amino acids as branching points
(b) Dendrimers functionalized at the periphery with peptide chains
(c) Grafted peptide dendrimers with either unnatural amino acids or organic groups as the branching core and peptides or proteins attached as surface functional groups. e.g. Beta Casomorphin (human)

III. Janus Dendrimers:

A Janus dendrimer has two sides; one side is polar (hydrophilic) and other side is non-polar (hydrophobic). These gives amphiphilic nature to the molecule.It is formed by linking two chemically distinct dendritic building blocks, thereby breaking the roughly spherical symmetry that characterizes most dendrimers. [34]

IV. Metallodendrimers:

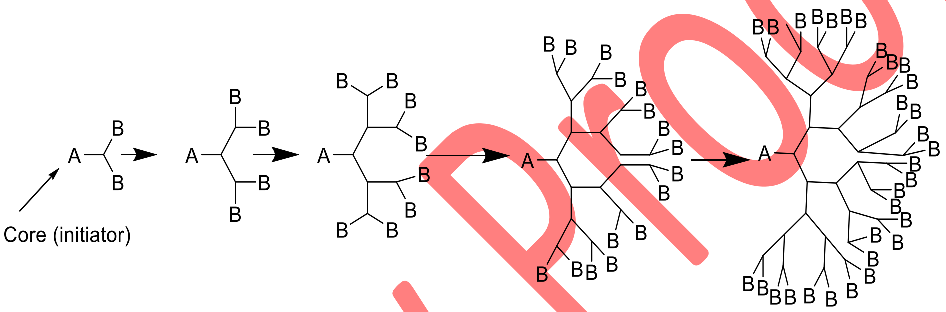
Metallodendrimers are complexes of dendrimers with metals. The metal site may be at the periphery, core and branching points of the dendrimer, or the metal may be encapsulated within the dendrimer. [35]

9. Synthesis Protocols:

A. Divergent Approach:

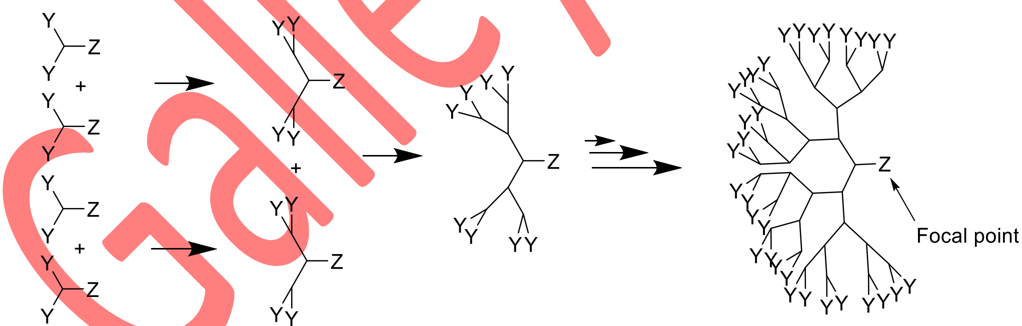
The synthesis of the dendrimer takes place in a stepwise manner starting from the core and constructing up the molecule towards the periphery using following two basic procedures:

i. Coupling of the monomer
ii. Deprotection or transformation of the monomer end-group to create a new reactive surface functionality.



B. Convergent Approach:

The dendrimer is synthesized stepwise, starting from the end groups and continuing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule.



C. Accelerated Approaches:

In response to the often tedious and purification intensive iterative processes, many researchers have sought accelerated approaches for synthesizing dendrimers by adopting combinations of the convergent and divergent strategies. [36]

The procedures include:

a) Multigenerational coupling:

i Hypercores:

Dendrons synthesized by convergent approach are coupled to the periphery of a dendritic core that already contains layers of branching units.

ii Hypermonomers:

These contain two or more layers of branching units, enabling the addition of multiple generations during each coupling step.

iii Double exponential growth:

This procedure requires a monomer with orthogonally masked focal and peripheral functionalities. The first generation dendron can be modified either at the focal point, to obtain the activated dendron, or at the periphery, to yield the first generation monomer. Coupling of the monomer and activated dendron yields a second generation dendron, which may likewise be activated at either the focal point or the periphery. Coupling of the resultant activated second generation dendron to the second generation hypermonomer affords a fourth generation dendron. Each successive repetition of these three steps (dendron activation, monomer activation and coupling) leads to a doubling of the generation number. [37]

b) Orthogonal syntheses:

The orthogonal approach involves convergent growth with two different monomers. The monomers, an AB2 and a CD2, must be carefully selected, such that the focal functionalities of each individual monomer will only react with the periphery of the other monomer (B couples only with C and D only with A), thereby removing the need for activation reactions. As a result of this synthetic design, each reaction in the synthesis adds a single generation to the dendron.

10. Factors Affecting:

A. Effect of Molecular Growth:

The conformational behaviour of a dendrimer upon growing to higher generations are determined by:

i. The molecular dimensions of the monomers– short monomers make quick production of chains within a small space.
ii. The flexibility of the dendrons.
iii. The ability of the end- groups to interact with each other.[38]

B. Effect of pH:

Structural behaviour of PAMAM dendrimers is depended upon pH.[2, 21]

i At Low pH (<4):

The interior gets increasingly "hollow". 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.

ii At Neutral pH (4-7):

Due to hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines, back-folding occurs.

iii At higher pH (pH>10):

At this pH, the conformation has a higher degree of back-folding as a consequence of the weak "inter-dendron" repulsive forces. [39]

C. Effect of Solvent:

The ability of the solvent to solvate the dendrimer structure is a very important factor when investigating the conformational state of a dendrimer. Molecular dynamics has been applied to study the variation of dendrimer conformation as a function of dendrimer generation in different solvents.

Dendrimers of all generations generally all experience a higher range of back-folding with 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. [8, 21]

D. Effect of Salt:

i High Concentration of Salts:-

- Has a strong effect on charged PPI dendrimers.
- Favours a contracted conformation of dendrimers with a high degree of back-folding.
- Similar to what is observed upon increasing pH or poor solvation.[8, 21]

ii Low Concentration of Salts:-

The repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure. [40]

E. Effect of Concentration:

In dendrimers with flexible structures the conformation is not only effected by small molecules like solvents, salts or protons, but may also be sensitive to larger objects, such as other dendrimers or surfaces which can have a great effect on the molecular density and conformation of the dendrimer.[8, 21]

11. Dendrimer-Drug Interactions:

Different dendrimer –drug interactions have been discovered, and they can be broadly subdivided into three types. [8, 41]

A. Simple Encapsulation:

- The factors that make it possible to directly encapsulate drug molecules into the macromolecule interior are:

(a) Ellipsoidal or spheroidal shape
(b) Empty internal cavities
(c) Open nature of the architecture of dendrimers

- These empty internal cavities are hydrophobic in nature, which make it suitable to interact with poorly soluble drugs through hydrophobic interactions.
- The nitrogen or oxygen atoms in the internal cavities can interact with the drug molecules by hydrogen bond formation.
- The internal cavities of dendrimers and drug molecules may interact with each other by

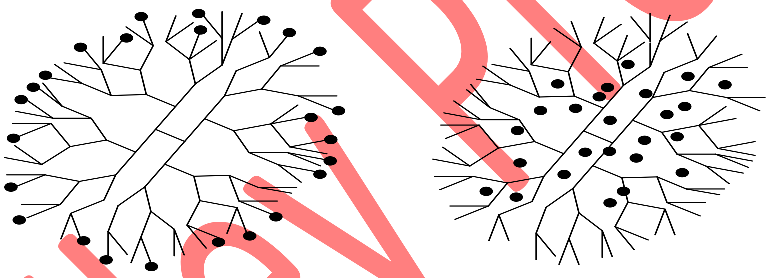
supramolecular interactions like physical encapsulation, hydrophobic interaction or hydrogen bonding.

B. Electrostatic Interaction:

- The functional groups with high density like amine groups and carboxyl groups on the surface of dendrimers have potency to enhance the solubility of hydrophobic drugs by electrostatic interaction.
- The G3 PAMAM dendrimer with an ammonia core is taken as an example. It has a much higher density amino group when compared with classical linear polymers.
- Non-steroidal anti-inflammatory drugs with carboxyl groups, including ibuprofen, ketoprofen, diflunisal, naproxen and indomethacin, have been widely been complexed with dendrimers by electrostatic interactions.
- Some anticancer and antibacterial drugs are also incorporated by this kind of interaction.
- The common property of these drug molecules is that they are weakly acidic drugs with carboxyl groups in the molecules.

C. Covalent Conjugation:

- The factor that makes dendrimer appropriate for the covalent conjugation of several drugs with relevant functional groups is presence of large numbers of functional groups on the surface.
- The drug is covalently bound to dendrimers and its release occurs via chemical or enzymatic cleavage of hydrolytically labile bonds.
- The covalent attachment of drugs to the surface groups of dendrimers through chemical bonds affords better control over drug release which facilitates the tissue targeting and controlled drug delivery.



Covalent conjugation   Simple encapsulation

D. Mechanism of Drug Delivery through Dendrimers:
There are broadly two mechanisms for drug delivery:[42]

- ➢ By in vivo degradation of drug dendrimer covalent bonding which is based on presence of appropriate enzymes or an environment capable of cleaving the bonds.[42]
- ➢ By releasing drug due to changes in physical environment such as pH, temperature.

12. Characterization:

A.	**Spectroscopy and Spectrometric Methods**	**Spectroscopy and spectrometric methods of characterization of dendritic polymer are as follows:**
	Mass Spectrometry (MS)	Helps in determination of the molecular weight, the structural defects in dendrimers, the polydispersity or the purity. It also allows the confirmation of the monomer assembly in the branches from the fragmentation pattern.[43]
	Nuclear Magnetic Resonance (NMR) Spectroscopy	Both mono (1H-, 13C-NMR) and bidimensional (2D-NOESY, 2D-TOCSY, DOSY, etc.) experiments are widely used to characterize the synthesis of dendrimers, molecule conjugations, conformational changes, group mobility, etc.

		15N-NMR has been also used to identify their selective protonation first on the surface of the second generation, then at the core and then at the level of the first generation.[44] Chemical shift titration experiments provide information on the interaction properties between dendrimer and guests, and can be used for the calculation of binding parameters and the spatial conformations within the dendrimer-guest complexes.[45]
	Fluorescence Spectroscopy	Fluorescence spectroscopy gives useful information about size and shape of dendrimers and their interaction with drugs.[46,47]
	Electron Paramagnetic Resonance (EPR)	It can widely and precisely inform about dendrimer structure and their interaction with other molecules such as proteins and drugs by using spin probes.[48]
	Infrared and Raman Spectroscopy	Infrared spectroscopy is mainly used for routine analysis of the variations in the dendrimer synthetic process.[44] FTIR and FT-Raman spectroscopy provides exclusive precise information on the structure of nano scale materials.
	UV-Vis Spectroscopy	This technique has been widely applied to monitor dendrimers production as the intensity of the absorption band is directly relative to the number of chromophoric units.[49]
B.	**Chromatographic Techniques**	**Chromatographic techniques of characterization of dendritic polymer are as follows:**
	Gel Permeation Chromatography (GPC)	This technique is usually used to find information on the composition of dendrimers, including their polydispersities.[50]
	High-Performance Liquid Chromatography (HPLC)	HPLC gives useful information on the homogeneity of dendrimers and dendrons and also their impurities. HPLC provided a quantitative assessment of G5 PAMAM dendrimer defects, identifying, isolating and characterizing the major structural defects of this system when combined with other techniques, such as potentiometric titration and mass spectrometry. Reversed-phase HPLC is carried out to confirm purity of the dendrimer and also to detect structural changes.[51]
C.	**Scattering Techniques**	**Scattering techniques of characterization of dendritic polymer are as follows:**
	Quasi-Elastic Neutron Scattering (QENS)	QENS accurately demonstrated the local motion of dendrimer segments. Reported an augmented local motion at increasing molecular charges.
	Small Angle Neutron Scattering (SANS)	This methodology reveals accurate information of the interior part of the entire dendrimer. It has been used to calculate the molecular weight of PPI and PAMAM dendrimers and also the location of the end groups by labeled them.[52]
	Small-Angle X-ray Scattering (SAXS)	SAXS was used to characterize the single-particle scattering elements formed by different species of dendrimers. It was also useful to inspect the advancement of intramolecular organizations of PAMAMs, producing maturation from “star” to “sphere” organizations.[53]
	Dynamic Light Scattering (DLS)	DLS is widely employed to analyse the structure of macromolecules. DLS, in combination with other techniques, was used to assess the interactions between cationic (G3, G4, and G5) and anionic (G4.5) (PAMAM) dendrimers, revealing that the formation of anionic-cationic dendrimer aggregates is an enthalpy driven process.[54]
D.	**Microscopy**	**Microscopy of characterization of dendritic polymer are as follows:**
	Atomic Force Microscopy (AFM)	AFM permits the characterization of the surface topography of dendrimers adsorbed onto a surface such as silica.

	Scanning Tunnelling Microscopy (STM)	This technique has also been used to characterize several dendrimer conjugates, in order to determine their precise size.[55] STM permits the production of high-resolution images and a rigorous determination of the lateral dimension of single dendrimers.
E.	**Electrophoretic Techniques**	Dendrimers carring multiple charges can be studied by electrophoretic techniques.[56] Pulse Acrylamide Gel Electrophoresis (PAGE) and capillary electrophoresis (CE) provide useful information about purity, homogeneity or electrophoretic mobility. The combination of capillary electrophoresis and mass spectrometry provides the opportunity to detect closely related compounds and isomers.[57,58] Electrophoretic techniques are also commonly used to characterize different dendrimer conjugates, such as dendriplexes.
F.	**Other Types of Techniques**	**Other types of techniques of characterization of dendritic polymer are as follows:**
	X-ray Diffraction	Dendrimers are usually amorphous solids with lack of long-range order in the condensed phase. This is the reason why X-ray diffraction is generally an unsuccessful technique to exactly determine the chemical composition, size and shape of dendrimers. However, some authors have determined the structure of several dendrimers.
	Acid-Base Titration	Dendrimer acid-base titration has been used to get information about their behavior at different pH values.

13. Applications:

A. Pharmaceutical Applications:

i. Dendrimers in Oral Drug Delivery:

Dendrimers with featured properties may act as potential carriers for orally controlled release systems by conjugating or encapsulating drug molecules to them. They keep drug concentrations within the therapeutic range at the injured regions, and hence can simplify dosing schedules. Also, dendrimers can increase the solubility of these orally administrated drugs and even the stability of drugs in biological environments. [59] These macromolecules with bioadhesive properties have strong affinity for mucosa and can prolong the residence time of the orally administrated drug in contact with the intestinal epithelium. Moreover, dendrimers themselves can easily penetrate through intestinal membranes, and thus can enhance the oral absorption of low-penetration drugs. [60]

ii. Dendrimers in Transdermal Drug Delivery:

PAMAM dendrimers can improve either the water solubility or stability of hydrophobic drugs. These materials with hydrophilic outer shells and hydrophobic interiors, which accord with structural requirement of polymeric transdermal enhancers, are expected to act as effective penetration enhancers. [61]

iii. Dendrimers in Ocular Drug Delivery:

Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. The important compensation of dendrimer in ocular drug delivery is perseverance in corneal residence time, which can provide better bioavailability of drug, and initiate in the form of eye drops. Dendrimers facilitate in achieving improved bioavailability, sustained, controlled as well as targeted release of drug. [62]

iv. Dendrimers in Intravenous/ Intraperitoneal/ Intratumoral Drug Delivery:

Dendrimers can be used to enhance the solubility of the drugs. Administration of dendrimer through the IV route is safe and nontoxic. More than 60% of cationic dendrimer gets accumulated in the liver and slow rate of clearance is observed in the liver and slow rate of clearance is observed in the case of anionic dendrimers. [41]

v. Dendrimers in Pulmonary Drug Delivery:

Dendrimers have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers were reported to increase the relative bioavailability of Enoxaparin by 40 %. The positively charged dendrimer forms complex with enoxaparin, which was effective in deep vein thrombosis after pulmonary administration. [63]

vi. Dendrimers in Other Drug Delivery Routes:

There are various applications of dendrimers in other delivery routes also such as the delivery via rectal, vaginal, or nasal routes, etc. [64]

vii. Dendrimers for targeted drug delivery:

Dendrimers are nanosized, non-immunogenic, and hyper branched vehicles have ideal properties which are brought in application in targeted drug delivery system. Folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains possessed reasonable drug loading is one of the most effective cell-specific targeting agents with a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer.[37]

viii. Dendrimers for controlled release drug delivery:

Controlled drug delivery is one which delivers the drug at a predetermined rate, for locally or systemically, for a specified period of time. The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers which had been modified with PEG monomethyl ether chains attached to their surfaces.

ix. Dendrimers for sustained release drug delivery:

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects.

Ketoprofen-PAMAM dendrimer complex showed sustained release of ketoprofen with prolonged effect.

x. Dendrimers as Nano-Drug:

Poly (lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus.PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be potent antibacterial biocides against Gram positive and Gram negative bacteria.

xi. Preparation of prodrugs:

PAMAM dendrimer-propranolol prodrugs have been prepared by conjugating propranolol-N-chloroacetyl conjugate to G3 and lauroyl-G3 PAMAM. These prodrugs were used to bypass efflux transporters and to enhance the oral bioavailability of propranolol. [65]

xii. Dendrimers used for enhancing the solubility:

PAMAM dendrimers are conventional to have potential applications in increasing the solubility for drug delivery systems. [66]

xiii. Dendrimers in Gene Transfection:

Dendrimers can act as vectors in gene therapy. PAMAM dendrimers were the first establish to be helpful for transfection. PAMAM dendrimers mediated the high efficiency transfection of DNA into a variety of cultured mammalian cells, which was a function of both dendrimer-DNA ratio and diameter of the dendrimers. Transfection efficiency could be increased by covalent attachment of a water-soluble peptide to a dendrimer via a disulfide linkage or by mannosylated dendrimers/cyclodextrin conjugate. [67, 68]

xiv. Cellular delivery using dendrimer carrier:

Dendrimer-ibuprofen complexes entered the cells rapidly and more efficiently carry the complexes drug inside cell compared to pure drug. To reduce toxicity and enhance cellular uptake PAMAM dendrimers were surface engineered with lauryl chains.

B. Therapeutic Applications

i. Photodynamic therapy:

Photodynamic therapy depend on the activation of a photosensitizing agent with visible or near infrared (NIR) light. Upon excitation, a highly energetic state is formed which, upon reaction with oxygen, affords a highly reactive singlet oxygen capable of inducing necrosis and apoptosis in tumor cells. Dendritic delivery of PDT agents has been investigated within the last few years in order to improve upon tumor selectivity, retention, and pharmacokinetics. [69, 70, 71]

ii. Dendrimers for boron neutron capture therapy:

BNCT refers to the radiation generated from the capture reaction of low energy thermal neutrons by 10B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. This radiation energy has been used successfully for the selective destruction of tissue. Dendrimers are a very fascinating compound for use as boron carriers due to their well-defined structure and multivalency. The first example of boron containing PAMAM dendrimer was synthesized by Barth et al., 1994.

iii. Diagnostic Applications

Dendrimers as molecular probes:

Dendrimers are attractive molecules to use as molecular probes because of their different morphology and unique characteristics.

iv. Dendrimers as X-ray contrast agents:

The X-ray machine is one of the fundamental diagnostic tools in medicine and is applicable to numerous diseases. To obtain a high-resolution X-ray image, several diseases or organs, such as arterio-sclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent. Dendrimers are currently under investigation as potential polymeric X-ray contrast agents.

v. Dendrimers as MRI contrast agents:

A number of research groups have discovered the use of dendrimers as a new class of high molecular weight MRI contrast agents. [72]

C. Other Applications

i. Dendrimers in biomedical field:

Dendritic polymers have advantages in biomedical applications. These dendritic polymers are similar to protein, enzymes, and viruses, and are easily functionalized. Dendrimers and other molecules can either be attached to the periphery or can be encapsulated in their interior voids. Modern medicine uses a variety of this material as potential blood substitutes. [73]

ii. **Dendrimers for additives, printing inks and paints:**

Dendrimers can be used in toners material with additives, which required less material than their liquid counterparts. Using preservative in printing inks, dendritic polymers certify to uniform linkage of ink to polar and non-polar foils. Use of Dendrimer additives in the composition of the innovation is efficient for varying the surface characterization of thermo plastic resin after moulding. [75]

iii. **Dendrimers as Catalyst:**

Dendritic polymers have been used in large amount as catalyst. [74]

iv. **Dendritic sensors:**

Dendrimers are single molecules that can contain high numbers of functional groups on their surfaces. This characteristic makes them applied to where the covalent connection or close proximity of a high number of species is important. [76]

v. **Dendrimers in light harvesting material:**

An important research has been of great attention for designing molecules with controlled movement of charges. Most of the literature account shows direction towards energy funneling from the chromospheres in the periphery to other chromospheres at the core.

Some examples of commercially available dendrimer-based products [8]

DENDRIMER PRODUCTS	BRAND NAME	APPLICATIONS
Vivagel®	Star Pharma	Prevent the transmission of HIV and STDs Condom coating
Priostar®	Star Pharma	Targeted diagnostic Therapeutic delivery for cancer cells
Priofect®	Star Pharma	SiRNA & DNA transfection reagents
Starburst®	Star Pharma	Dendrimers commercial
Alert ticket™	US army Research Laboratory	Anthrax detecting agent
Startus CS®	Dade Behring	Cardiac marker
SuperFect®	Qiagen	Gene Transfection
NanoJuice™	EMD Chemicals	DNA transfection agent kit

14. Future Prospects:

Since the first dendrimers were synthesized a rapid growth of interest in the chemistry of dendrimers has been observed. The initial work concentrated on different approaches of synthesis and investigations of properties of the new class of macromolecules. Soon first applications appeared. Despite two decades since the discovery of dendrimers the multistep synthesis still requires great effort. Unless there is an important breakthrough in this field, only few applications for which the unique dendrimer structure is vital will pass the cost benefit test.

Though very few pharmaceutical products having dendrimers are available in market, the dendrimer technology holds great potential adding value to pharmaceutical products. [22]

Future development focuses on following aspects:

(a) Decreasing cost of synthesis of dendrimers so as to be applied extensively in membranes and other fields.

(b) Expanding application of membranes from hyper branched polymers to the fields of resources and environment.

(c) Developing new applications of dendritic polymers in other fields of membrane.

15. CONCLUSIONS

Dendrimers are expected to play an important role in the biological field of the 21st Century. Due to the exclusive approach of Dendrimers, they have improved physical and chemical properties. The elevated stage of control over the structural design of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds an ultimate carrier in biomedical application such as drug delivery, gene transfection and imaging. These properties construct the dendrimers a smart choice for drug delivery application and improve the solubility of poorly soluble drug. This review article of dendrimer provides basic information about drug carrier, clearly identifies the potential of these novel polymers and confirms the high buoyancy for the future of dendrimers in pharmaceutical field. These matchless physical and chemical properties of dendrimer have established immense versatilities in variety of applications. Also further studies are needed to recognize their absorption, uptake mechanisms by biological membranes and in-vivo stability. Dendrimers have successfully used in medicinal applications such as diagnostic tools and ultimately in drug delivery.

16. CONFLICT OF INTEREST

Authors declare no conflict of interest.

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