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Review Article

# Dendrimers as a Novel Approches for Drug Delivery System: A Review

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**ABSTRACT**

This review provides brief information concerning with the dendrimer, its properties, its synthesis, characterization and application in drug delivery. Dendrimer consist of well defined size, shape, molecular weight and monodispersity. These properties formulate the dendrimers a suitable carrier in drug delivery application. The unique architectural design of dendrimers, high degree of branching, multivalency, globular architecture and well defined molecular weight, clearly distinguishes these structures as unique and optimum nanocarriers in medical applications such as drug delivery, gene transfection, tumor therapy, diagnostics, etc. Synthetic approaches lead to a dendritic architecture with properties amenable to modifications of shape, size, polarity, surface properties and internal structure. Nanoparticle drug-delivery systems are the popular ones as are able to increase the selectivity and stability of therapeutic agents. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications.



## INTRODUCTION

Novel drug delivery system aims to deliver the drug at a rate directed by the needs of the body during the period of treatment, and target the active entity to the site of action. A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery [1], dendrimer carriers being one of them. Dendrimers, a new class of polymeric materials are nanosized, radially symmetrical with well-defined homogenous and monodisperse structure consisting of tree-like atoms or branches. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behavior, dendrimers are suitable for a wide range of biomedical and industrial applications. These are versatile, well-defined, compartmentalized polymers with sizes and physicochemical properties resembling to those of biomolecules like proteins. A macromolecular drug-delivery system is a complex material in which a drug is attached to a carrier molecule such as a synthetic polymer, antibody, hormone or liposome [2].

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These hyper branched molecules were first discovered by Fritz Vogtle in 1978, Donald Tomalia and co-workers in the early 1980s, and at the same time, but independently by George R. Newkome. The word "dendrimer" originated from two words, the Greek word "dendron" meaning tree, and "meros" meaning part or unit. These might also be called as 'cascade molecules', but this term is not as much established as 'dendrimers' [3]. Dendrimers have gained a broad range of applications in supraemolecular chemistry, particularly in host- guest reactions and self-assembly processes. Dendrimers are characterized by special features that make them promising candidates for a lot of application. Dendrimers are highly defined artificial macromolecules, which are characterized by a combination of high number of functional groups and a compact molecular structure [4].

### History of Dendrimer

Dendrimers are an attractive exclusive class of polymers with controlled structure. A dendrimer is both a covalently assemble molecule and also a distinct nanoparticle. The first dendrimers be completed by divergent synthesis advanced by Fritz Vogtle in 1978 [5], R.G. Denkewalter at Allied Corporation in 1981 [6], Donald Tomalia at Dow Chemical in 1983 and in 1985, and by George Newkome in 1985 [7], In 1990 a convergent

synthetic approach was introduce by Jean Fréchet [8], A lot of research has already been completed by studying the different properties and application of dendrimers but a lot of researchers still believe it to be in its initial stages.

**Structure of Dendrimers**

A dendrimer is typically symmetric around the core (Fig.2), and often develops a three-dimensional morphology .In the view of polymer chemistry dendrimeres are perfect monodisperse macro molecules with regular highly branched three dimensional structures (Fig. 3) and consist of three architectural components like core, branches and end groups.[9, 10]

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure [11]. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the 'starburst effect [12]. For PAMAM dendrimer synthesis it is observed after tenth generation. The rate of reaction drops suddenly and further reactions of the end groups cannot occur. The tenth generation PAMAM contains 6141 monomer units and has a diameter of about 124 Å [13].

The increasing branch density with generation is also believed to have striking effects on the structure of dendrimers. They are characterised by the presence of internal cavities and by a large number of reactive end groups (Fig. 4). Dendritic copolymers are a specific group of dendrimers. There are two different types of copolymer.

Segment-block dendrimers are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one polyfunctional core molecule.

Layer-block dendrimers consist of concentric spheres of differing chemistry. They are the result of placing concentric layers around the central core. Hawker and Fréchet[14], synthesised a segment- block dendrimer which had one ether-linked segment and two ester-linked segments. They also synthesised a layer-block dendrimer. The inner two generations were ester-linked and the outer three etherlinked. The multi-step synthesis of large Quantities of higher generation dendrimers requires a great effort. This was the reason why Zimmerman's group applied the concept of self-assembly to dendrimer synthesis [15]. They prepared a wedgelike molecule with adendritic tail in such a manner that six wedge-shaped subunits could self-assemble to form a cylindrical aggregate. This hexameric aggregate is about 9 nm in diameter and 2 nm thick. It has a large cavity in the centre. The six wedges are held together by hydrogen bonds between carboxylic acid groups and stabilised by Vander Waals interactions. However, the stability of the hexamer is affected by many factors. The aggregate starts to break up into monomers when the solution is diluted, when the aggregate is placed in a polar solvent like tetrahydrofuran (THF), and when the temperature is high. The hexamer's limited stability is due to its noncovalent nature.

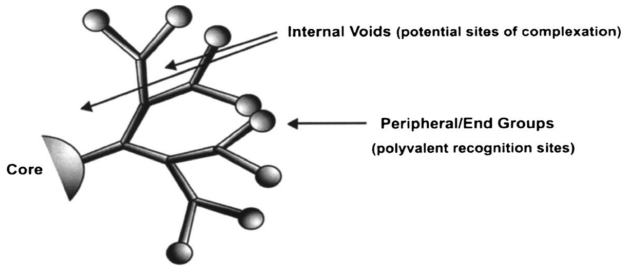


**Figure1:** Three main parts of a dendrimer: the core, end-groups, and subunits linking the two molecules.

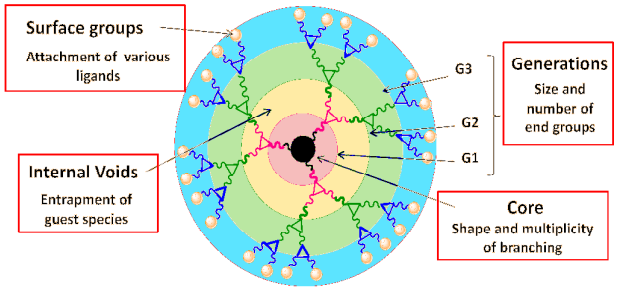


**Figure 2:** Schematic representation if generation of two dendrimres

**Ideal Properties of Dendrimers**

- Dendrimers are monodisperse macromolecules, unlike linear polymers.
- Dendrimers have some unique properties because of their globular shape and the

presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior.

- Dendrimers have been applied in in vitro diag- nostics. Dade Internati-onal Inc. (U.S.A.) has introduced a new method in cardiac testing. Proteins present in a blood sample bind to immunoglobulins which are fixed by dendrimers to a sheet of glass. The result shows if there is any heart (2.5 and 3.5) are weaker.
- Anionic dendrimers, bearing a carboxylate surface, are not cytotoxic over a broad concentration range. [16]
- Dendrimers are Inert and non-toxic.
- It is Biodegradable.
- Non - immunogenic.
- Able to cross barriers such as intestine, blood-tissue barriers, cell membranes etc.
- Able to stay in circulation for the time needed to have a clinical effect.
- Able to target to specific structures.
- Compatible with guest molecules.
- Must protect the drug until it reaches to the desired site of action and release the drug. [17]

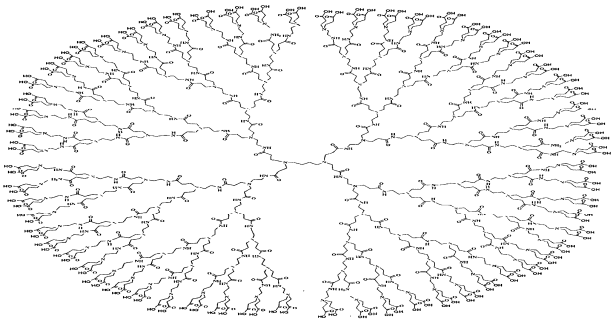

**Figure 3:** Highly branched three dimensional structures

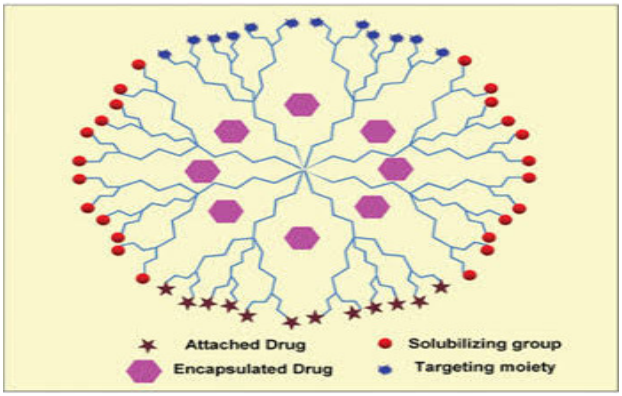


**Figure 4:** Dendritic box encapsulating guest molecules

**Synthesis of Dendrimers**

Dendrimers are just in between molecular chemistry and polymer chemistry. They relate to the molecular chemistry world by virtue of their step-by-step controlled synthesis, and they relate to the polymer world because of their repetitive structure made of monomers [18, 19, 20, 21]. The three traditional macromolecular architectural classes (i.e. linear, cross-linked and branched) are broadly recognized to generate rather polydisperse products of different molecular weights. In contrast, the synthesis of dendrimers offers the chance to generate monodisperse, structure controlled macromolecular architectures similar to those observed in biological systems [22, 23]. Dendrimers are generally prepared using either a divergent method or a convergrnt one [24]. In the different methods, dendrimer grows outward from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups, giving the first- generation dendrimer. Then, the new periphery of the molecule is activated for reaction with more monomers.

**1. Divergent method** – This is mechanical reaction. The dendrimer is assembled from multifunctional core, which is extends outward by a series of reactions (fig.5). Each step of the reaction must be driven to full completion to prevent mistakes in the dendrimer, which can cause trailing generations (some branches are shorter than the others). Such impurities can impact the functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small. [25].

**2. Convergent method** - Dendrimers generally made of small molecules that end up at the surface of the sphere and reactions proceed inward and are evenly attached to the core this method (fig. 6) makes it much easier to remove impurities and shorter branches along the way, so that the final dendrimer is more monodisperse. [25]

**3. Hypercores' and 'Branched Monomers' growth** - Linkage of the oligomeric species in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation Dendrimers. [26]

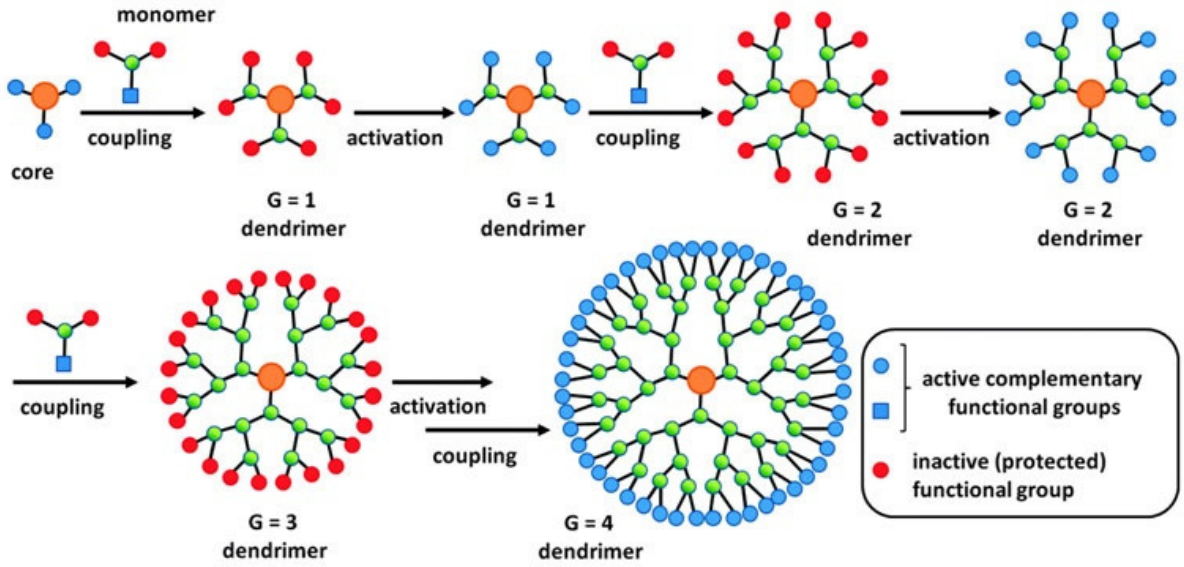


**Figure 5:** Divergent Dendrimer Growth

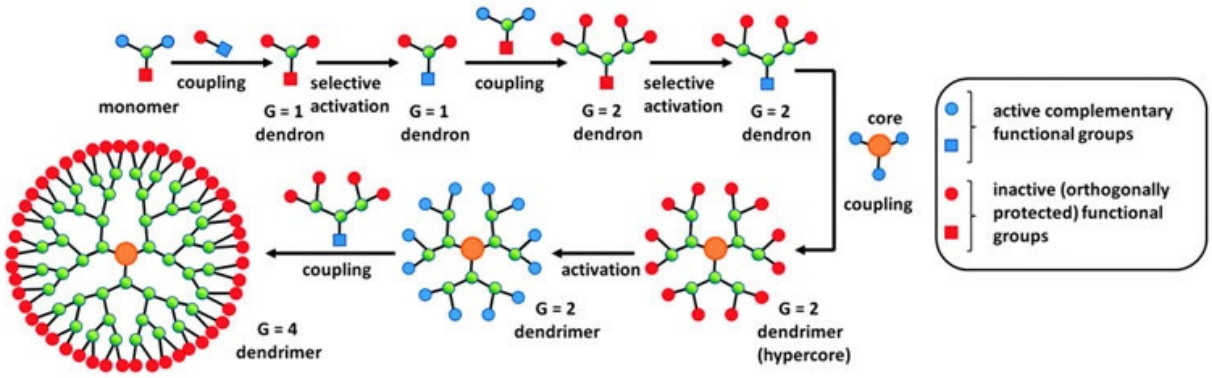


**Figure 6:** Convergent Dendrimer Growth

**4. Double Exponential' or mixed growth** - In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. [27, 28]

**Types of Dendrimers**

**1. Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) -**

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, lectronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honeycomblike networks with nanoscopic PAMAM and OS domains. [29, 30]

**2. Poly (amidoamine) dendrimers (PAMAM)**

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. When looking at the structure of the highgeneration in two-dimensions, star like pattern observed. They are commercially available as methanol solutions and ingeneration G 0-10 with 5 different core type and 10 functional surface groups. [31, 32]

**3. Poly (Propylene Imine) dendrimers (PPI)**

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary trispropylene amines present in interior portion. It

commercially available up to G5, and wide applications in material science as well as in biology.10 PPI dendrimers are available as AstramolTM. [33]

**4. Chiral dendrimers**

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

**5. Liquid crystalline dendrimers**

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

**6. Tecto dendrimer**

Tecto Dendrimer are composed of a core dendrimer, perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

**7. Hybrid dendrimers**

Hybrid dendrimers are hybrids (block or graft polymers) of dendritic and linear polymers. Obtained by complete monofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic selforganized lattices that are less readily available from other modified dendritic structures.

**8. Multilingual Dendrimers**

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

**9. Micellar Dendrimers** -

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

**Applications of Dendrimers**

Specific properties such as unparalled molecular uniformity, multifunctional surface and presence of internal cavities makes dendrimers suitable for a variety of high technology uses and are as follows**:**

**A) Pharmaceutical Application**

**1. Dendrimer in ocular drug delivery** [34, 35]

PAMAM dendrimers with carboxylic or hydroxyl surface groups, improving residence time and enhance bioavailability of pilocarpine in the eye.

**2. Dendrimers in pulmonary drug delivery** [36]

Positively charged PAMAM dendrimers (G2 and G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.

**3. Dendrimer in transdermal drug delivery** [37,38]

Dendrimers are able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently due to its highly water soluble and biocompatible nature. For example improving the drug permeation through the skin when PAMAM dendrimer complex with NSAIDs like Ketoprofen, Diflunisal and enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application.

**4. Dendrimer in oral drug delivery** [39, 40]

Oral drug delivery studies using the human colon adenocarcinoma cell line, which have indicated that lowgeneration PAMAM dendrimers cross cell membrane through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Increase in the cytotoxicity and permeation of dendrimers when increase in the concentration and generation.

**5. Dendrimers in targeted drug delivery** [41]

Dendrimers have ideal properties which are useful in targeted drug-delivery system. For example PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively.

**6. Dendrimers for controlled release drug delivery** [42]

Encapsulation of 5-fluorouracil into PAMAM dendrimers(G=4) modified with carboxy methyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity. Controlled release of the Flurbiprofen achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers.

**Table 1:** Characterizations of dendrimers by various methods [26]

| S. No. | Techniques | Applications |
|---|---|---|
| 1 | UV-Vis method | Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units. |
| 2 | Infra-red spectroscopy | For routine analysis of the chemical transformations Occurring at the surface of dendrimers. |
| 3 | Near Infra-red spectroscopy | Used to characterized delocalize π-π stacking interaction between end group of modified PANAM. |
| 4 | Fluorescence | The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers. |
| 5 | Mass spectroscopy | Chemical ionization or fast atom bombardment can be used only for the characterization of small Dendrimers whose mass is below 3000. Electrospray ionization can be used for Dendrimers able to form stable multicharged species. |
| 6 | X-ray diffraction | This technique should allow precise determination of the chemical composition, structure, size and shape of dendrimers. |
| 7 | Microscopy Transmission microscopy | Electron or light produce images that amplify the original, with a resolution ultimately limited by the wavelength of the source. |
| 8 | Scanning microscopy | The image is produced by touch contact Q at a few angstroms of a sensitive cantilever arm with sample. Ex. Atomic force microscopy |
| 9 | Chromatography according to size. | Size exclusive or gel permeation chromatography allows the separation of molecules according to size. |
| 10 | Electrical techniques A. Electron paramagnetic resonance<br>B. Electrochemistry | Quantitative determination of the substitution Efficiency on the surface of PANAM dendrimers. It give information about the possibility of interaction of electro active end groups |
| 11 | Electrophoresis | Used for the assessment of purify and homogeneity of several type of water soluble dendrimers |
| 12 | Rheology, Physical properties A | Used as analytical probe of the morphological structure of dendrimers. |
| 13 | Differential scanning calorimetry | Used to detect the glass transition temperature which depends on thy molecular weight, entanglement and chain composition of polymers. |
| 14 | Dielectric spectroscopy | Gives information about molecular dynamic processes |

### 7. Dendrimers in gene delivery [43]

Dendrimers are extensively used as non-viral vector for gene delivery. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

### 8. Dendrimer as solubility enhancer [44]

Dendrimers are unimolecular micellar nature, due to have hydrophilic exteriors and hydrophilic interiors and form covalent as well as non-covalent complexes with drug molecules and hydrophobes, and enhance its solubilisation behaviour.

### 9. Cellular delivery using dendrimer carrier [45]

PAMAM dendrimers with lauryl chains to reduce toxicity and enhance cellular uptake, for example Dendrimer– ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells.

### 10. Dendrimers as Nano-Drugs [46]

Dendrimers as Nano-Drugs, useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs) when Poly(lysine) dendrimers modified with sulfonated naphthyl groups. Show potent antibacterial biocides against Gram positive and Gram negative bacteria when PPI dendrimers with tertiary alkyl ammonium groups attached to the surface and Chitosan– dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications.

**11. Dendrimers as bio mimetic artificial proteins** [47, 48]

Dendrimers are often referred to as "artificial proteins" due to their dimensional length scaling, narrow size distribution, and other bio mimetic properties. For examples PAMAM family, they closely match the sizes and contours of many important proteins and bio assemblies like insulin (3 nm), cytochrome C (4 nm), and haemoglobin (5.5 nm) are approximately the same size and shape as ammonia-core PAMAM dendrimers generations 3, 4 and 5, respectively. Generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes (form stable complexes with histone clusters to condense and store DNAwithin the nucleosome of cells.) and generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of biological cells.

**12. Dendrimers as nano-scaffolds** [49, 50]

Reducing the interaction with macromolecules from the body defense system, and imaging tags due to an excellent platform provided for the attachment of cellspecific ligands, solubility modifiers, and stealth molecules by dendrimer surface. For examples folate– PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron-capture treatment of cancer tumors.

**B) THERAPEUTIC APPLICATION**

**1. Dendrimers in photodynamic therapy (PDT)** [51]

Cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue. For example. The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes.

**2. Dendrimers for boron neutron capture therapy (BNCT)** [52]

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. Due to their well defined structure and multivalency, Dendrimers are a very fascinating compound for use as boron carriers.

**C) DIAGNOSTIC APPLICATION**

**1. Dendrimers as molecular probes** [53]

Due to their distinct morphology and unique characteristics, use as molecular probes. For Example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular probe, because of their large surface area and high density of surface functionalities**.**

**2. Dendrimers as X-ray contrast agents** [54,55]

Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin are used to obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary etc**.**

**3. Dendrimers as MRI contrast agents** [56, 57]

Introduction of target specific moieties to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer contrast agents, for example folate conjugated Gd (III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

**D. Current and Potential Applications of Dendrimers** [58, 59]

- One dendrimer molecule has hundreds of possible sites to couple to an active species. This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side affects of medications on healthy cells.
- Modification of cell-cell interactions and gene expression (e.g.: alteration of transcription factors binding to DNA)
- New carrier system for drug delivery (gels, selfassociating systems)
- 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, radio ligands, imaging agents, or pharmaceutically active compounds.
- Delivery of Nucleic acids, Encapsulated drugs and Covalently linked drugs.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.
- Vaccines against bacteria, viruses and parasites.
- Diagnostic reagents in: serodiagnosis (systems with surface ligands), Biosensor systems (systems containing dyes, reactive

molecules) magnetic resonance imaging (e.g.: gadolinium adducts).

**Dendrimer Based Products** [60, 61, 62]

Several dendrimer based products have already been approved by the FDA and some in Phase II clinical trials. Various dendrimer based products are:

(1) Alert ticket for Anthrax Detection
(2) Priofect™, Priostar™ and Starburst for targeted diagnostic, therapeutic delivery for cancer cells
(3) SuperFect for Gene Transfection
(4) Stratus CS for Cardiac Marker
(5) Vivagel for preventing HIV

## CONCLUSION

Dendritic polymers are expected to play a key role as enabling building blocks for nanotechnology during the 21st century, a rapid increase of interest in the chemistry of dendrimers has been observed since the first dendrimers were synthesised. The chemical synthesis and modification of the dendrimer resulted in a wide range of variation in properties. Dendrimers, due to its superior architecture; high level of branching, globular architecture and molecular weight, prove to be a novel and reliable method of drug delivery. Future work is necessary to find out cost effective synthetic strategies with minimum efforts and the relationship between dendrimer-drug molecules for effective commercial utilization of this technology. The review clearly illustrates the different aspects of dendrimers as novel drug delivery system and there will be accretion in the dendrimers seen as drug delivery systems with the advent of more and more dendrimers used for it. Due to their exclusive manner dendrimers 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.

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