Review Article

# DENDRIMERS

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**ABSTRACT**

Dendrimer are highly branched molecule having a well defined size, shape, molecular weight, and monodispersity as compared to linear polymer. Dendrimer have tree like shape consist of central core, branches and terminal group. The bioactive agents may either be encapsulated into the interior of the dendrimers or they may be chemically attached or physically adsorbed onto the Dendrimer surface. Dendrimer have wide application in pharmaceutical field, in gene transfection, as a diagnostic agent, as blood substituent, as solubility enhancer. Surface-modified dendrimers themselves may act as nano-drugs against tumours, bacteria and viruses. This review focus on structure, property, method of synthesis, various method of characterisation, application of Dendrimer, formulation of Dendrimer.

**Keywords:** Dendrimer, Convergent, Divergent.

## INTRODUCTION

The term dendrimer originates from Greek word **'Dendron'** meaning a tree. The synonym for Dendrimer is **'Arborols'** (from latin word 'arbor') also meaning a tree and **'Cascade molecule'**. Dendrimers are repetitively branched molecules consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped having diameters in the 2 to 10 nm range. Dedrimer having very low polydispersity and high functionality. A dendron usually contains a single chemically addressable group called the focal point (branching points).

### History[1,3]

The first dendrimers Synthesis done by divergent synthesis approaches by Fritz Vögtle in 1978, R.G. Denkewalter at Allied Corporation in 1981, Donald Tomalia at Dow Chemical in 1983 and in 1985, and by George Newkome in 1985. In 1990 a convergent synthetic approach was introduced by Jean Fréchet.

The first synthesized dendrimers were polyamidoamines (PAMAM). At the same time Newkome group independently reported synthesis of similar macromolecules they called 'arborols'.

### Merit[4,5]

1. Dendrimers particle size in nanometer in range of 1-100 nm, hence easily crosses cell membrane.
2. Clearance through Reticulo-Endothelial System (RES) reduced due to small size.
3. Dendrimer is perfect carrier for unstable drug which protected in core.
4. It shows monodispersity.
5. Dendrimer improves solubility of poorly soluble drug.
6. Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.

### Demerit[49]

1. It is not suitable for oral drug delivery because drug–dendrimer complex not cross gut wall.
2. Drug–dendrimer construct is considered as new chemical entity so that clinical testing for new construct required.

### Structure[6-9]

Dendrimer built from starting material is nitrogen atom. Then carbon and other element added by chemical reaction.

### Dendrimer composed of[6-8]

- An initiator core.
- Interior layers (generations) composed of repeating units, radically attached to the interior core.
- Exterior (terminal functionality) attached to the outermost interior generations.

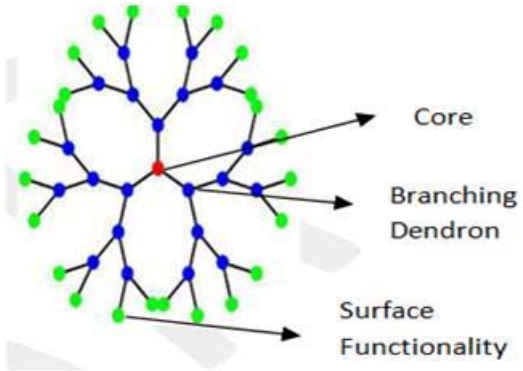


**Figure 1**: Dendrimer

**Component of Dendrimer Structure**

- **Pincer**

The outer shell of dendrimers contains a varying number 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 pincers in the Poly propylene Imine (PPI) and Poly amido amine (PAMAM) dendrimers becomes half the number of the surface groups present. (because in these dendrimers the chain divides into two chains in each focal point).

- **Shell**

The dendrimer shell is the generation space (i.e the homo-structural spatial segment) between the focal points.

Outer shell: The space between the last outer branching point and the surface is outer shell.

Inner shells: Dendrimer interior is inner shell.

- **Generation**[6,9]

It is the hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points).

Generation number:

Generation number is the number of focal points present in the dendrimer counting from the core towards the dendrimer surface.

5th generation Dendrimer:

A dendrimer having five (5) focal points when moving from the centre towards the periphery is signified as the 5th generation dendrimer and abbreviated as G5-dendrimer.

**Ex:** A 5th generation polypropylene imine(PPI) is abbreviated to a 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 substituents are not considered as focal points. Intermediates formed during the dendrimer synthesis are sometimes termed as half-generations.

**Ex:** The PAMAM dendrimers terminated with carboxylic acid

- **End-group**

End groups are generally called as the surface group of the dendrimer or terminal group. Dendrimers terminated with amine end-groups are named as amino-terminated dendrimers. Solubility of dendrimer in solvent depend upon end group.

**Types of Dendrimer**[10-13]

PAMAM Dendrimer

PAMAMOS Dendrimer

PPI Dendrimer

Tecto Dendrimer

Chiral Dendrimers

Hybrid Dendrimers

Liquid Crystalline Polymers

Amphiphilic Dendrimers

Micellar Dendrimers

Multiple Antigen Peptide Dendrimers

Frechet-Type Dendrimers

Multilingual Dendrimers

**Pamam Dendrimer**[10]

**Poly (amidoamine) dendrimers / starburst Dendrimer**

**Method of synthesis:** Divergent starting from ammonia or ethylenediamine initiator core reagents. PAMAM dendrimers are commercially available as methanol solutions. Starburst name to PAMAM dendrimer due to the starlike pattern observed when looking at the structure of the high generation dendrimers of this type in two dimensions.

**Use:** Material Science, Biomedicine Computer toners.

**Eg:** DendritechTM

**Pamamos Dendrimer**

**Radially layered poly (amido amine organosilicon) Dendrimers**

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers.

**Structure**

**End group:** Hydrophobic organosilicon (OS)

**Interior part:** Hydrophilic, nucleophilic polyamidoamine

**Method of synthesis:** Convergent and Divergent.

**Use:** Nano-lithography, Electronics, Photonics, Chemical catalysis Precursor for honeycomb like network preparations.

**Eg:** SARSOX

**PPI Dendrimer**

**Poly-Propylene Imines/DAB/POPAM**

Is the oldest known dendrimer type developed initially by Vögtle.

**Structure**

**End group:** Primary amines.

**Interior part:** Numerous tertiary trispropylene amines.

PPI dendrimers are commercially available up to G5.

POPAM is alternative name to PPI. It stands for Poly (Propylene Amine).

It also called as DAB-dendrimers where DAB refers to the core structure, which is usually based on Diamino butane.

**Method of synthesis:** Divergent.

**Use:** Material science and biology.

**Eg:** Asramol by DSM

**Tecto Dendrimer**

**Structure:** It Composed of a core dendrimer with multiple dendrimers at its periphery.

**Method of synthesis:** Divergent

**Use:** Diseased cell recognition, Diseased state drug delivery diagnosis, Reporting location to outcome of therapy.

**Eg:** Stratus® CS Acute Care TM, Starburst®, Mercapto

**Chiral Dendrimer**

**Structure:** Chilarity is based on construction of constitutionally different but chemically similar branches to a chiral core.

**Method of synthesis:** Convergent.

**Use:** Biomedical applications, chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.

**Eg:** chiral dendrimers derived from pentaerythritol.

**Hybrid Dendrimer**

**Structure:** These are hybrids (block or graft polymers) of dendritic and linear polymers obtained by complete mono functionalization of the peripheral amines of a "zero-generation".

Polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic self-organized lattices that are less readily available from other modified dendritic structures.

**Method of synthesis:** Divergent.

**Use:** Biomedicals, Molecular electronics, Nanophotonics, Sensing

**Eg**: Hybrid dendritic linear polymer, Polysilsesquioxanes.

**Liquid Crystalline Dendrimer**

**Structure:** A highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour.

They consist of mesogenic (liq. crystalline) monomers.

**Method of Synthesis:** Divergent.

**Use:** Science and Engineering.

**Eg:** Mesogen functionalized carbosilane dendrimers

**Amphiphil Dendrimer**

**Structure:** Unsymmetical globular dendrimers built with two segregated sites of chain end. One half is electron donating and the other half is electron withdrawing.

**Method of Synthesis:** Divergent.

**Use:** Structure-directing agent, Use as polar part, cell and gene transfection.

**Eg:** SuperFect, Hydraamphiphiles and bola-amphiphiles

**Micellar Dendrimer**

**Structure:** These are unimolecular micelles of water soluble hyper-branched polyphenylenes.

**Method of Synthesis:** Divergent

**Use:** Biological and medical applications, Drug delivery, Imaging agent.

**Eg:** Beclomethazone dipropionate, NX-200, Magnevist®

**Multiple Antigen Peptide Dendrimer**

This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications.

**Structure:** It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points.

**Method of Synthesis:** Convergent.

**Use:** In vaccines and diagnostic research. Biological applications.

**Eg:** VivaGel

**Frechet Type Dendrimer**[10,11]

**Structure:** Dendrimes having carboxylic acid groups as surface groups and containing poly-benzyl ether hyperbranched skeleton.

**Method of Synthesis:** Convergent

**Use:** Drug carrier, Purifiers, Organic synthesis, detecting agent, drug delivery.

**Eg:** Dendron azides, PriostarTM

**Properties of Dendrimer**[14-17]

**Monodispersity**

Dendrimer are monodisperse having same size. Dendrimer synthesis is specifically controlled which reduces size variation unlike linear molecule synthesis produces random structure and high size variation. Dendrimer synthesized from convergent method having high monodispersity than other method.

Most of structural defect occur during formation of high generation dendrimer because of incomplete reaction, steric hinderance problem.

**Technique of characterisation for Monodispersity**

Mass spectroscopy

Size exclusion chromatography

High performance liquid chromatography

Transmission electron microscopy

Gel Electrophoresis

**Solubility**

Functional group present on surface decide solubility of dendrimer. Hydrophilic group on surface is soluble in polar solvent like water. Hydrophobic group on surface soluble in non-aqueous solvent.

Internal cavity carries hydrophobic drug and improves solubility. In a solubility test with tetrahydrofuran as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester.

**Size and Shape**

Size of Dendrimer is in nanometer. Due to less particle size not only dendrimer easily cross the cell membrane but also clearance from body is reduced. Dendrimers show some significantly improved physical and chemical properties because of their molecular architecture, as compared to traditional linear polymers. Shape of dendrimer depend upon generation of dendrimer.

***Lower generation***

Open planer elliptical shape.

***Higher generation***

Compact spherical shape.

**Rheological Property**

In solution linear chains exist as flexible coils, in contrast dendrimers form a tightly packed ball which influences its rheological properties. Dendrimer having less viscosity than linear polymer. As molecular mass increases intrinsic viscosity increases upto $4^{th}$ generation dendrimer then decreases.

**Crystallinity**

Dendrimer are non-crystalline and amorphous materials

**Immunogenicity**

Dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) they become non-immunogenic or less immunogenic.

**Cytotoxicity**

Cytotoxicity of dendrimer depend upon core of dendrimer but it also affected by functional group present on surface of dendrimer having amino (-NH2) group at surface shows cytotoxic property but this also depend upon generation of dendrimer and concentration. Higher generation dendrimers being the most toxic.

**Method of Synthesis**[18-24]

The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.

1. Divergent Method
2. Convergent Method
3. Double Exponential and Mixed Method
4. Hypercores and Branched Monomers Growth

**Divergent Method**

Characteristic: Dendrimer formation start from core.

Merit:-Lagre quantity of dendrimer produced by this method.

Demerit:-To prevent problem during synthesis large quantity of reagent required.

Product purification is very tedious task.

Diagram:

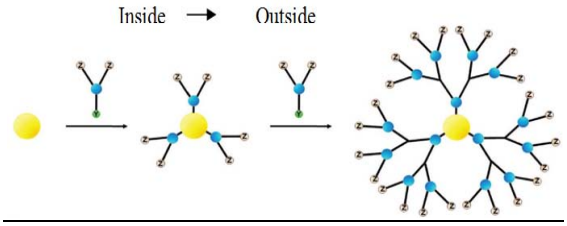


**Figure 2**: Divergent method of dendrimer synthesis

**Convergent Method**

Charactristics: Dendrimer formation from Surface.

Merit:-Defects in the final structure are less. Product easily purified.

Demerit:-Due to steric hindrance higher generation dendrimer cannot be formed.

Diagram:

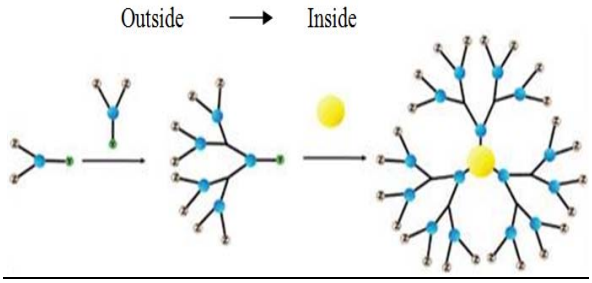


**Figure 3:** Convergent method of dendrimer synthesis

**Double exponential and mixed method**

Charactristics:-This method both Divergent and Convergent method used.

Merit:-Rapid growth technique for linear polymers, Fast method.

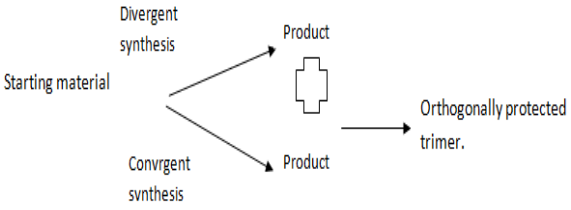


Diagram:

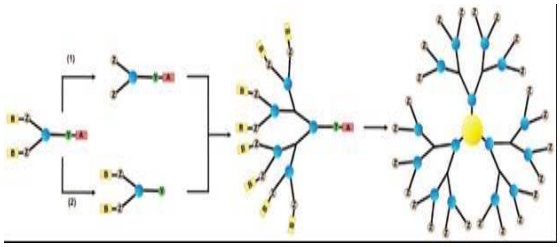

**Figure 4:** Double exponential method of Dendrimer synthesis.

**Hypercores and branched monomers growth**

**Characteristics**

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers.

**Merit**

Fewer steps, Higher yields.

**Factor Affecting Dendrimer Synthesis[4,25]**

There are various factors which affect dendrimer synthesis are following:

a) Incomplete addition reaction.

b) Intermolecular cyclization.

c) Fragmentation.

d) Solvolysis of terminal functionalities.

**Factors Affecting Dendrimer Properties[26-28]**

**Table 1:** Factors affecting Dendrimer properties

| S. No | Factor | Level | Effect |
|---|---|---|---|
| 1 | **Effect of pH** | Low | -Structural behaviour of PAMAM dendrimers is depended upon pH.<br>-At low pH (< 4) the interior is getting increasingly **hollow.**<br>-Repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior increases at high generation. |
| | | Neutral | -At neutral pH, back-folding occurs which may be a consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. |
| | | High | -At higher pH (pH>10) the dendrimer contract as the charge of the molecule becomes neutral, acquiring a more spherical (globular) structure, where the repulsive forces between the dendrimer arms and between the surface groups reaches minimum. |
| 2 | **Effect of Salt** | High | -High concentration of salt have 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 solvation. |
| | | Low | -The repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure. |
| 3 | **Effect of Solvent** | | -The solvation power of any solvent to solvate the dendrimer is a very important parameter.<br>-Dendrimers of all generations generally exhibit a larger extent of back-folding with decreasing solvent quality.<br>-The dendrimer arms induce a higher molecular density on the dendrimer surface.<br>-NMR studies performed on PPI dendrimers concluded that a nonpolar Solvent like benzene, poorly solvates the dendrimers favouring intramolecular interactions between the dendrimer segments and back-folding. |
| 4 | **Effect of Concentration of Dendrimer** | | -Small angle X-ray scattering (SAXS) experiments performed on PPI dendrimers (G4, G5) in a polar solvent like methanol show that the molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted.<br>-This molecular contraction may minimize the repulsive forces between the dendrimer molecules and increase the ability of the dendrimers to exhibit a more tight intermolecular packing. |

**Table 2:** Characterisation of dendrimer

| S. No | Name of Method | Subtype | Characteristic | Application |
|---|---|---|---|---|
| 1 | **Spectroscopy and Spectrophotometry** | Ultra-violet–visible (UV–vis) | -Range 200-800nm.<br>-Detect presence of Conjugation. | -Synthesis.<br>-Conjugation due to change in lamda max,<br>-Reaction rate |
| | | Infra-red (IR) | -Range 0.8-1000µm<br>-Detect Functional group | -Synthesis,<br>-Functional group,<br>-Conjugation and<br>-Drug-dendrimer interaction. |
| | | Nuclear Magnetic Resonance (NMR)<br>A) NOSY<br>B) One-dimensional (1D) and two-dimensional (2D)<br>NMR<br>C) REDOR | No and type of of proton | -Synthesis<br>-Conjugation<br>chemistry [shielding deshielding effects shifts in peak]<br>-Number of protons.<br>Quantitative determinations of internuclear distances for nuclei n different parts of the dendrimer molecule.<br>conformation of a melamine dendrimer<br>PAMAM<br>Dendrimers |
| | | Mass spectrometry<br>MALDI-TOF-MS<br>ESI-MS | Determine mass to charge ratio | -Determining the molecular weight.<br>-Structural defects in dendrimers.<br>-Determination of the polydispersity.<br>-Purity of dendrimers. |
| | | Raman Spectroscopy | Study vibrational, rotational motion in dendrimer. | -Structure of Dendrimer.<br>-Librations of terminal groups in dendrimers.<br>-Interaction between PAMAM dendrimer with lipid membranes. |
| | | Fluorescence spectroscopy | Emission method | -Interaction between the drug and dendrimers.<br>-Size and shape of Molecules |
| | | Atomic force microscopy (AFM) | | -Structure.<br>-Interaction of the different dendrimer therapeutics with a lipid bilayer,<br>Behavior of the dendrimer agents |
| | | X-ray Absorption Spectroscopy (XAS) | | -Structural information.<br>-Electronic structures |
| | | X-ray Photoelectron Spectroscopy | | -Elemental composition<br>-Empirical formula<br>-Chemical state.<br>-Thickness of one or more thin layered dendrimers |
| 2 | **Scattering techniques** | Small angle X-ray scattering (SAXS) | | - Average radius of gyration (Rg) in solution.<br>-The intensity of the scattering as a function of angle also provides information on the arrangement of polymer segments. |
| | | Small angle neutron scattering (SANS) | | - Radius of gyration |

| | | | | |
|---|---|---|---|---|
| | | | | -More accurate information about Internal structure than small angle X ray scattering.<br>-Information about location of End group. |
| | | Laser light scattering (LLS) | | Hydrodynamic radius of dendrimers. |
| **3** | **Rheology and Physical properties** | Intrinsic viscosity | | Used as analytical probe morphological structure of dendrimers |
| | | Differential scanning calorimetry (DSC) | -Melting point<br>-Intereaction of drug and excipient | Detection of Glass Transition Temperature |
| **4** | **Miscellaneous** | Sedimentation | | -For lactosylated PAMAM dendrimers,<br>-measurements of dipole moments for PMMH dendrimer. |

## Formulation of Dendrimers[30]

**Table 3:** Formulation of dendrimer

| S. No | Brand Name | Type of Dendrimer | Company | Application |
|---|---|---|---|---|
| **1** | Vivagel | Multiple Antigen | Star pharma | HIV prevention |
| **2** | Alert ticket | PAMAM | US army research laboratory | Anthrax Detection |
| **3** | SuperFect | Ampiphilic | Qiagen | Gene Transfection |
| **4** | Stratus CS | Tecto | Dade Behring | Cardiac Marker |
| **5** | Priofect™, Priostar™ | Tecto | Starphrma | Targeted diagnostic, therapeutic delivery for cancer cells |
| **6** | Avidimer | | DOW | Cancer prevention, treament |
| **7** | Dendritic | PAMAM | | |
| **8** | Astramol | PPI | DSM | |
| **9** | Starburst | PAMAM | | Targeted diagnostic, therapeutic delivery for cancer cells |

## Encapsulation of Drugs within the Dendritic Architecture[29-34,16,17]

### Encapsulation

Due to the ellipsoidal or spheroidal shape, empty internal cavities, and open nature of the architecture of dendrimers it is possible to directly encapsulate guest molecules into the macromolecule interior. These empty internal cavities are hydrophobic in nature, which make it easy 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.

### *PEGylated dendrimers*

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer which is hydrophobic in nature and PEG to provide a hydrophilic shell around hydropobic core of dendrimer to form a unimolecular micelle. Due to Hydrophilic core of PEG clearance of dendrimer from body is reduced. PEG having high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications.

### *Dendritic box*

Jansen described the synthesis of poly (propylene imine) dendrimers based dendritic boxes. During the synthetic process, guest molecules could be entrapped within the cavities of the dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication. Through end group modification with a bulky amino acid derivative to yield a dense and rigid chiral shell with solid-phase properties and a flexible core capable of entrapping molecules.

### *Cored dendrimers*

Zimmerman and co-workers synthesised cored dendrimers that resemble hollow nanospheres, encapsulate substances made them candidates for delivery vehicle. Encapsulation was achieved by postsynthetic modification of the dendritic architecture. The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the

structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups.

***Unimolecular micelles***

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. **Eg.** synthesised a symmetrical, four directional saturated hydrocarbon cascade polymer containing 36 carboxylic acid moieties with a neopentyl core. It was shown that lipophilic probes were located within the lipophilic infrastructure of the dendritic structures and it was concluded that the polymers exist as single molecules capable of molecular inclusion and therefore act as unimolecular micelles.

**Interaction of Dendrimer Drug[35-36]**

***Electrostatic Interaction***

The high density of functional groups like amine groups and carboxyl groups on the surface of dendrimers have potential applications in enhancing the solubility of hydrophobic drugs by electrostatic interaction. **Eg.** The G3 PAMAM dendrimer with an ammonia core. It has a much higher amino group density 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 have also been reported to be 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 molecule.

***Covalent Conjugation***

The presence of large numbers of functional groups on the surface of dendrimers makes them suitable for the covalent conjugation of numerous drugs with relevant functional groups.

In this case, the drug is covalently bound to dendrimers and its release occurs via chemical or enzymatic cleavage of hydrolytically labile bonds.

Covalent attachment of drugs to the surface groups of dendrimers through chemical bonds affords better control over drug release, facilitating the tissue targeting and controlled drug delivery.

**Characterisation of Dendrimer[4,5,16,17,30,37]**

1. Spectroscopic and Spectrophotometric Method.
2. Scattering Method.
3. Rheology and Physical Method.
4. Miscellaneous Method.

**Application of Dendrimer**

***Blood Substitution[38]***

Dendrimers are used as blood substitutes. Their steric bulk surrounding a heme mimetic centre significantly slows degradation compared to free heme, and prevents the cytotoxicity exhibited by free heme.

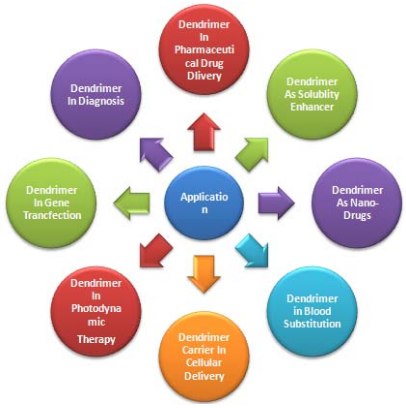


**Figure 5:** Application of dendrimer

**Drug Delivery**

***Oral Drug Delivery[24,39]***

Oral route most widely used route Strong acid and enzyme present in stomach causes degradation of drug. Dendrimer interior is hollow so it provide good site for drug entrapment. This entrapment increases solubility as well as stability of drug.

**Eg.** PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging. Dendrimer provide protective layer reduces the effect of acid and enzyme.

***Ocular Drug Delivery[40]***

The intraocular bioavailability of topically applied drugs is extremely poor. These occur mainly due to drainage of the excess fluid via nasolacrimal duct and elimination of the solution by tear turnover. Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery.

**Eg.** Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability by synthesizing a hydrogel composed of PEGylated dendrimers that contain ocular drug molecules attached to the dendrimers efficiently deliver the drugs to the eye.

***Pulmonary Drug Delivery[41]***

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 Enoxapariby 40 %. The

positively charged dendrimer forms complex with enoxaparin, which was effective in deep vein thrombosis after pulmonary administration.

### *Transdermal Drug Delivery*[42]

Dendrimers have found applications in transdermal drug delivery systems. Generally, drugs have hydrophobic in nature resulting in low water-solubility that inhibits efficient delivery into cells. Dendrimers has been found to improve solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently.

**Eg : 1.** PAMAM dendrimer complex with (e.g. Ketoprofen, Diflunisal) have been reperted to improve the drug permeation through the skin as penetration enhancers. Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. Enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application was reported to be effective.

**2.** Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers.

### *Antineoplastic Drug Delivery*[43,44]

The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h). In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. Combined, these factors lead to the selective accumulation of macromolecules in tumor tissue –a phenomenon termed the "Enhanced Permeation and Retention" (EPR) effect. Therefore, the anticancer drug doxorubicin was covalently bound to this carrier via an acid-labile hydrazone linkage.

The cytotoxicity of doxorubicin was significantly reduced (80–98%), and the drug was successfully taken up by several cancer cell lines.

### Nano-drugs[45]

- Eg Poly(lysine) dendrimer modified with Sulfonated naphthyl groups useful in Herpes simplex virus Prevent/reduce transmission of HIV other sexually transmitted diseases (STDs).
- PPI dendrimer modified with tertiary alkyl ammonium groups attached to the surface shows potent antibacterial biocides against Gram positive and Gram negative bacteria.
- Poly(lysine) dendrimer modified with mannosyl surface groups are Inhibitors of the adhesion of E. coli to horse blood cells in a haem agglutination assay.
- Chitosan–dendrimer hybrids useful as antibacterial agents.

### Gene Transfection[46,47]

Dendrimers can act as **vectors**, **in gene therapy**. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus.

### *SuperFectTM*

SuperfectTM is transfection reagent consisting of activated dendrimers is commercially available. Activated dendrimers can carry a larger amount of genetic material than viruses. SuperFect–DNA complexes are characterized by high stability and provide more efficient transport of DNA into the nucleus than liposomes. The high transfection efficiency of dendrimers may not only be due to their well-defined shape but may also be caused by the low pK of the amines (3.9 and 6.9). The low pK permit the dendrimer to buffer the pH change in the endosomal Compartment.

PAMAM dendrimers functionalized with cyclodextrin showed luciferase gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and cyclodextrin.

### Solubility Enhancers[48-50]

Poor solubility and hydrophobic nature of drugs/bioactives major limitation in applications of drug delivery and formulation development. Dendrimers represent a novel type of polymeric material that has generated much interest in many diverse areas due to their unique structure and properties. Dendrimer-mediated solubility enhancement mainly depends on many factors such as pH, temperature, etc. Available literature suggests that ionic interaction, hydrogen bonding, and hydrophobic interactions are the possible mechanisms by which a dendrimer exerts its solubilizing property.

### Effect of Generation Size

Chauhan used G4-NH2, G4-OH, and G4.5 ester terminated PAMAM dendrimers for solubility enhancement of Indomethacin.

It was observed that at pH 7 aqueous solubility of Indomethacin increased in following order: G4-NH2 > G4-OH, > G4.5.

Three different mechanisms for solubility enhancement were proposed for these generations having different terminal functionalities.

### *Amine terminated dendrimers*

Electrostatic interactions between the terminal amine groups of dendrimers and the carboxylic group of drug.

### *Hydroxy terminated dendrimers*

Weak hydrogen bonding.

***Ester-terminated dendrimers***

Molecular encapsulation.

**Effect of pH**

The protonation of nitrogen whether at periphery or at dendrimer interiors is influenced by pH. Recent reports reveal attempts to study the effect of pH on the acid-base properties of these nitrogens and the impact on solubility enhancement.

**Eg:** Devara konda found that Nifedipine solubility increased linearly with increasing concentration of amine-terminated PAMAM dendrimers at pH 7 and pH 10 but not at pH 4.

**Effect of Temperature**

Temperature is one of the most important factors influencing solubility.

$$solublity \propto \frac{1}{Tempreture}$$

As tempreture increase Solubility decreases.

**Photodynamic Therapy (PDT)[15,16,17,51,52]**

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes. Photo sensitive dyes have been incorporated into dendrimers and utilized in PDT devices. This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue.

**Boron Neutron Capture Therapy (BNCT)[53,54]**

Their well defined structure and multivalency, dendrimers are a very fascinating compound for use as boron carriers

**Diagnostic Application**

***Molecular probes[55]***

Due to their distinct morphology and unique characteristics, use as molecular probes.

**Eg.** 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.

***X-ray contrast agents[56,57]***

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.

**MRI contrast agents[15,58,59]**

Introduction of target specific moiety to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer contrast agents.

**Eg:** folate conjugated Gd (III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

**Cellular Drug Delivery[12,15]**

Kennan et al. studied the dynamics of cellular entry into A549 human lung epithelial carcinoma cells of a range of PAMAM dendrimers (G4-NH2, G3-NH2, G4-OH, PEGlayted G3 [G3-PEG]) and a hyper branched polymer (polyol). G4-NH2and G4-OH entered cells more rapidly than did G3-NH2, polyol or G3-PEG. It was suggested that the rapid entry of G4-NH2 might be a result of the cationic nature of the amine surface groups, which may interact electrostatically with negatively charged epithelial cells and enter via fluid phase pinocytosis. The lower rate of cellular entry of G3-NH2com-pared with G4-NH2 may be a result of fewer surface charges on the G3-NH2 dendrimer. Because polyol and G3-PEG do not have cationic surface groups, their cellular entry may result from non-specific adsorption to the cell membrane and subsequent endocytosis. 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. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

## CONCLUSION

Most of drug are class 2 drug having problem of less solubility which improved by dendrimer drug delivery by entrapment of drug in core of dendrimer. Dendrimer also increases stability of drug. Drug incorporated into dendrimer by simple encapsulation, covalent interaction, electrostatic interaction. Dendrimer given along with Polyethylene glycol (PEG) having less cytotoxicity. Property of Dendrimer like monodispersity, molecular weight, architecture improves drug delivery. Dendrimer not only used in drug delivery but also having wide application like gene transfection, diagnostic application.

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