



## DENDRIMERS: A NOVEL POLYMER FOR DRUG DELIVERY

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### ABSTRACT

Dendrimers are a unique class of synthetic macromolecules having highly branched, three dimensional, nanoscale architecture with very low polydispersity and high functionality. These features have made their application in nanotechnology, pharmaceutical and medicinal chemistry particularly attractive. This review briefly discusses the various aspect of dendrimer including properties, preparation of dendrimers types, characterization, and their use as pharmaceutical, therapeutic, diagnostic agent and their potential for applications in drug delivery. The biocompatibility of dendrimers follows patterns known from other small particles. Synthetic approaches lead to a dendritic architecture with properties amenable to modifications of shape, size, polarity, surface properties and internal structure. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached i.e. conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. This review clearly demonstrates the various application of dendrimer and indeed substantiates the high hopes for future.

**Keywords:** Dendrimers, PAMAM Dendrimer, Synthesis, Characterization of dendritic polymer.

### 1. INTRODUCTION<sup>1-3</sup>

A dendrimer is generally described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers have often been referred to as the "Polymers of the 21<sup>st</sup> century". Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers<sup>1</sup>. He synthesized the first "cascade molecules". In 1985, Donald A. Tomalia synthesized the first family of dendrimers<sup>2</sup>. The word "dendrimer" originated from two words, the Greek word **dendron**, meaning tree, and **meros**, meaning part. At the same time, Newkome's group<sup>3</sup> independently reported synthesis of similar macromolecules. They called them **arborols** from the Latin word 'arbor' also meaning a tree. The term **cascade molecule** is also used, but 'dendrimer' is the best established one. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.

Dendrimer oligonucleotide are representative of a new segment of polymer science, dendrimers are precisely defined, synthetic nonmaterial's that are approximately 5-10 nanometers in diameter. Dendritic polymers or dendrimers provide a route to create very well-defined nanostructures suitable for drug solubilization applications, delivery of DNA and oligonucleotide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system<sup>1</sup>.

Dendrimers are core-shell nanostructures with precise architecture and low polydispersity, which are

synthesized in a layer-by-layer fashion (expressed in 'generations') around a core unit, resulting in high level of control over size, branching points and surface functionality. The ability to tailor dendrimer properties to therapeutic needs makes them ideal carriers for small molecule drugs and biomolecules. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular<sup>2</sup>.

### 2. STRUCTURE:<sup>4-6</sup>

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex.

Dendrimers possess three distinguished architectural components<sup>4,5</sup>, namely

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



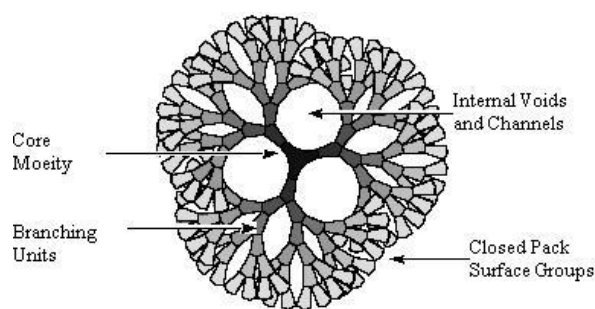


Figure 1: The Dendritic Structure

## 2.1 Components of a Dendrimer Structure

### 2.1.1 Generation

It is the hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points). The number of focal points when going from the core towards the dendrimer surface is the generation number. That is a dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer. Here, we abbreviate this term to simply a G5-dendrimer, e.g. a 5th generation polypropylene imine is abbreviated to a "G5-PPI-" dendrimer. The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented here "G0". The core structure thus presents no focal points, as hydrogen substituents are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted half-generations, a well-known example is the carboxylic acid-terminated PAMAM dendrimers.

### 2.1.2 Shell

The dendrimer shell is the homo-structural spatial segment between the focal points, the "generation space". The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred to as the dendrimer interior.

### 2.1.3 Pincer

In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface. In PPI and PAMAM dendrimers the number of pincers is half the number of surface groups (because in these dendrimers the chain divides into two chains in each focal point).

### 2.1.4 End-group

It is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "amino-terminated dendrimers".

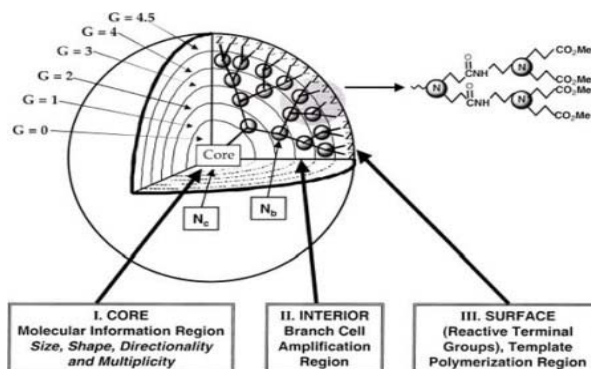


Figure 2: Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface.

## 2.2 Types of Dendrimers<sup>4, 7-9</sup>

### 2.2.1 Pamam Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation  $10^7$  (a molecular weight of over 9, 30,000 g/mol) have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, usually as methanol solutions. **Starburst dendrimers** is applied as a trademark name for a subclass of PAMAM dendrimers based on a tris-amino ethylene-imine core. The name refers to the starlike pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

### 2.2.2 Pamamos Dendrimer

Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

### 2.2.3 PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle.<sup>8</sup> These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine), which closely resembles the PPI abbreviation. In addition, these dendrimers are also sometimes denoted "DAB-

dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

#### 2.2.4 Tecto Dendrimer

These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

#### 2.2.5 Multilingual Dendrimers

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

#### 2.2.6 Chiral Dendrimers

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

#### 2.2.7 Hybrid Dendrimers Linear Polymers

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

#### 2.2.8 Amphiphilic Dendrimers

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

#### 2.2.9 Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

#### 2.2.10 Multiple Antigen Peptide Dendrimers

It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, e.g. vaccine and diagnostic research.

#### 2.2.11 Fréchet-Type Dendrimers

It is a more recent type of dendrimer developed by Hawker and Fréchet<sup>6,8</sup> based on poly-benzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving 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.

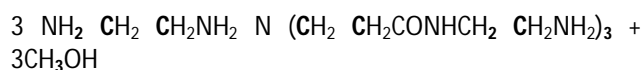
### 3. SYNTHESIS<sup>10, 12, 13</sup>

The synthesis used for dendrimer preparation permit almost entire control over the critical molecular design parameters such as size, shape, surface/interior chemistry, flexibility, and topology. Many dendrimer syntheses rely upon traditional reactions, such as the

Michael reaction or the Williamson ether synthesis whilst others involve the use of modern techniques and chemistry, such as solid-phase synthesis, organo-transition-metal chemistry, organosilicon chemistry, organo-phosphorus chemistry, or other contemporary organic methodologies. The choice of the growth reaction dictates the way in which the branching should be introduced into the dendrimer. Branching may either be present in the building blocks as is more often the case or it can be created as a function of the growth reaction, as is the case with the poly (amidoamine)s and the poly (propylene imine)s<sup>12</sup>.

#### 3.1 'Divergent' Dendrimer Growth<sup>10, 13</sup>

The synthetic methodology employed in the early dendrimer synthesis came to be known as the 'divergent' approach. This name comes from the way in which the dendrimer grows outwards from the core, diverging into space. Starting from a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers. The two steps can be repeated. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is doubled. Divergently grown dendrimers are virtually impossible to isolate pure from their side products. The synthetic chemist must rely on extremely efficient reactions in order to ensure low polydispersities. The first synthesized dendrimers were **polyamidoamines (PAMAMs)**. They are also known as **starburst dendrimers**. Ammonia is used as the core molecule & In the presence of methanol, it reacts with methylacrylate and then ethylenediamine is added:<sup>13</sup>



At the end of each branch there is a free amino group that can react with 2 methyl acrylate monomers and 2 ethylenediamine molecules. Each complete reaction sequence results in a new dendrimer generation. The number of reactive surface sites is doubled with every generation the mass increases more than twice<sup>10</sup>.

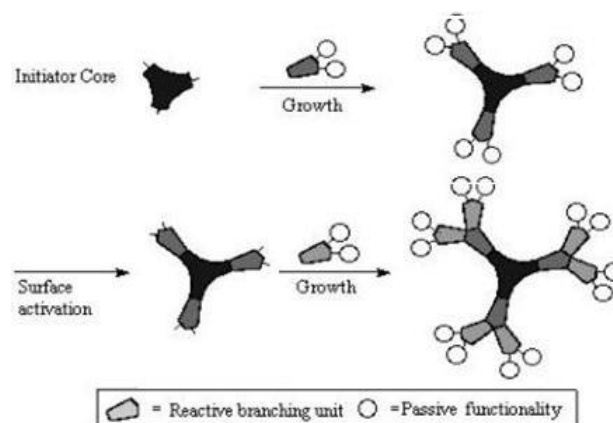


Figure 3: Divergent Dendrimer Growth





### 3.2 'Convergent' Dendrimer Growth<sup>10,13</sup>

The 'convergent' approach was developed as a response to the weaknesses of divergent synthesis. Convergent growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step<sup>13</sup>. The convergent methodology also suffers from low yields in the synthesis of large structures. The convergent growth method has several advantages:

1. Relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised.
2. Possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecules.
3. Approach does not allow the formation of high generation dendrimer because steric problems occur in the reactions of the dendrons and the core molecule<sup>10</sup>.

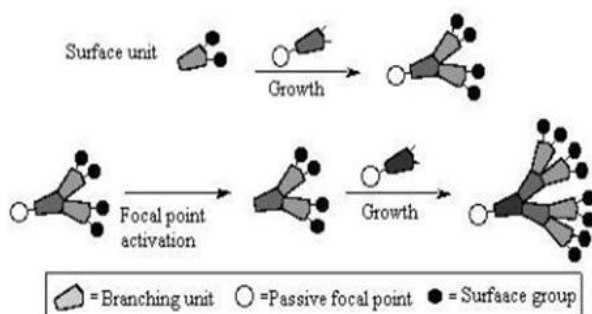


Figure 4: Convergent Dendrimer Growth

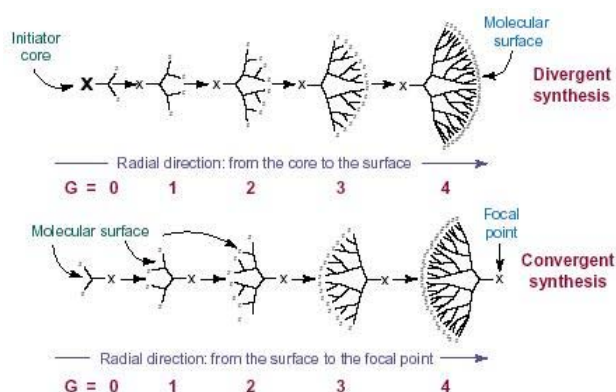


Figure 5: Two principle synthetic methods for constructing dendritic macromolecules (dendrons): (a) the divergent method, in which the synthesis begins from a polyfunctional core and continues radially outwards by successive stepwise activation and condensation, (b) the convergent method in which the synthesis begins at what will be the periphery of the final macromolecule and proceeds inwards.

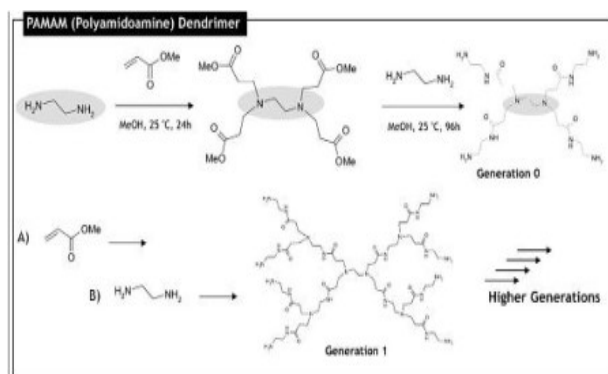


Figure 6: Graphical presentation of PAMAM dendrimers from core to generation G=7 showing the linear increase in diameter and exponential growth of the number of surface groups<sup>12</sup>.

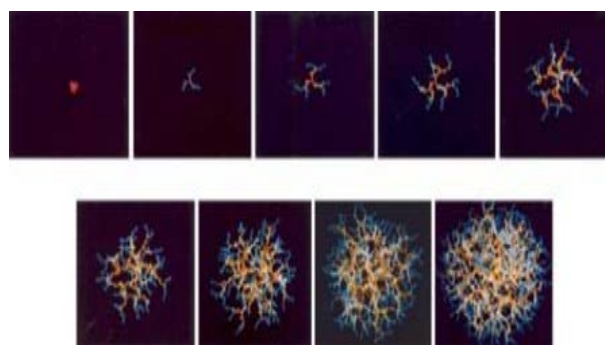
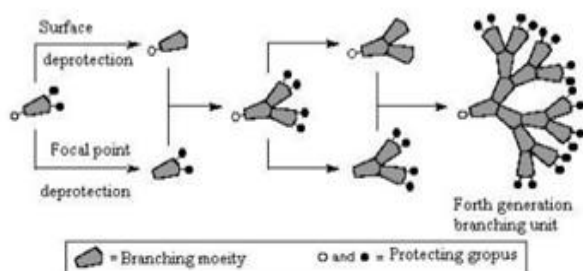


Figure 7: Synthesis of commercially available PAMAM dendrimer.

### 3.3 'Double Exponential' And 'Mixed' Growth<sup>10,13</sup>

The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' growth. A schematic representation of double exponential and mixed growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB<sub>2</sub> monomer with orthogonal protecting groups for the A and B functionalities. This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material<sup>10</sup>.

These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. The double exponential methodology provides a means whereby a dendritic fragment can be extended in either the convergent or the divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings<sup>13</sup>.

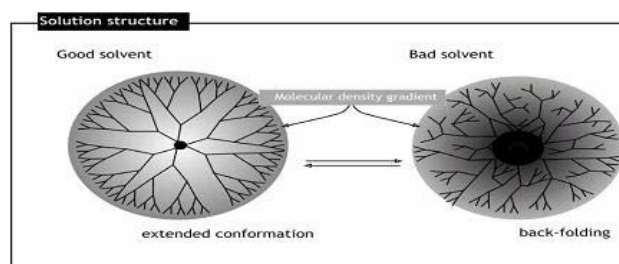


**Figure 8:** Double Exponential and Mixed Growth

#### 4. PROPERTIES OF DENDRIMERS <sup>4, 11, 15-36</sup>

The classical polymerization process, which results in linear polymers, is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis. Dendrimers are monodisperse macromolecules, unlike linear polymers. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Lower generation dendrimers, which are large enough to be spherical but do not form a tightly packed surface, have enormous surface areas in relation to volume. In contrast to linear polymers the intrinsic viscosity of dendrimer solutions does not increase linearly with mass but shows a maximum at a specific generation and then begins to decline <sup>11, 15</sup>. Such behaviour is unlike that of linear polymers. This is likely to be because of the way in which dendrimer shape changes with generation, i.e. lower generations adopt a more open planar-elliptical shape with transition to a more compact spherical shape for higher generations. The presence of many chain ends is responsible for high solubility and miscibility and for high

reactivity. In the structure of dendrimer (Fig.10) the molecular density is theoretically highest in the periphery of the dendrimers. It has been suggested that back folding of the terminal branches leads to a more uniform or even reverse density profile <sup>16</sup> (Fig.10). In nature tree-like structures have evolved to maximize the exposed surface area, e.g. to maximize the light exposure/number of leaves of a tree. In a similar fashion dendritic architecture creates molecules where a large proportion of the groups are exposed at the surface and which can have very high molecular surface to volume ratios (up to 1000 m<sup>2</sup>/g). The presence of numerous terminal groups in dendrimers facilitates multiple simultaneous interactions of surface groups with the solvent, surfaces or other molecules and, as a consequence, dendrimers tend to show high solubility, reactivity, and binding.



**Figure 9:** Dendrimer conformation.

This multivalency is of particular importance for biomedical applications. The multiple interactions between surface amines and nucleic acid phosphates are also important for the formation of dendrimers and DNA complexes. Dendrimers' solubility is strongly influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester. A marked difference was also observed in chemical reactivity.

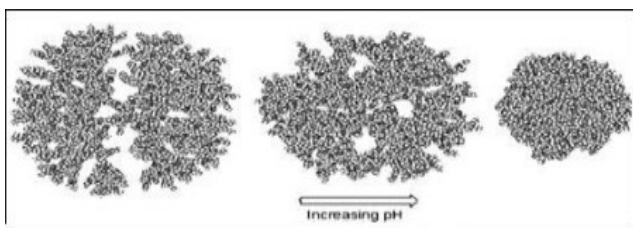
**Table 1:** Properties of Dendrimer and linear polymers

Sr. No.	Property	Dendrimers	Linear Polymers
1	Structure	Compact, Globular	Not compact
2	Synthesis	Careful & stepwise growth	Single step polycondensation
3	Structural control	Very high	Low
4	Architecture	Regular	Irregular
5	Shape	Spherical	Random coil
6	Crystallinity	Non-crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7	Aqueous solubility	High	Low
8	Nonpolar solubility	High	Low
9	Viscosity	Non linear relationship with molecular weight	Linear relation with molecular weight
10	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydisperse

## 4.1 Effect of Various Factors on the Properties of Dendrimers<sup>17, 18</sup>

### 4.1.1 Effect of pH

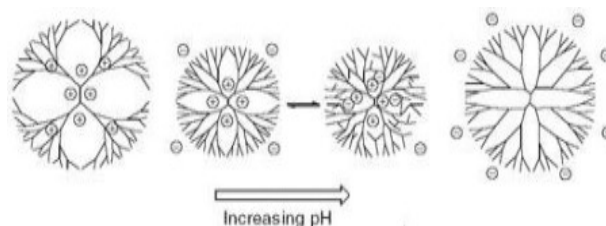
**Amino-terminated PPI and PAMAM dendrimers<sup>17</sup>** have basic surface groups as well as a basic interior. For these types of dendrimers with interiors containing tertiary amines, the low pH region generally leads to extended conformations due to electrostatic repulsion between the positively charged ammonium groups. Applying molecular dynamics to predict the structural behaviour of PAMAM dendrimers as a function of pH show that the dendrimer has an extended conformation, based on a highly ordered structure at low pH (pH<4). At this pH, the interior is getting increasingly "hollow" as the generation number increases as a result of repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior. At neutral pH, back-folding occurs which may be a consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. At higher pH (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 a minimum. At this pH, the conformation has a higher degree of back-folding as a consequence of the weak "inter-dendron" repulsive forces (Figure 11).<sup>18</sup>



**Figure 10:** Three-dimensional structure of a G6-PAMAM dendrimer, under different pH.

When looking at the pH-dependent conformational changes of **PPI dendrimers having acidic (carboxylic acid) end-groups**, the picture is somewhat different compared to what is observed for their amino-terminated counterparts (Figure 12). Small angle neutron scattering (SANS) and NMR measurements of self-diffusion coefficients at different pH values show that at pH 2 the dendrimer core has the most extended conformation due to the electrostatic repulsion between the positively charged protonated tertiary amines, leading to a large radius of the core, whereas the dendrimer reaches its minimum radius at pH 6, where the amount of positively charged amines equals the amount of negatively charged carboxylic groups (isoelectric point) resulting in a "dense core" conformation more subjective to back-folding. Thus, at pH 6 some degree of back-folding occurs as a result of attractive interactions between the negatively charged surface carboxy-groups and the positively charged tertiary amines in the inner shells of the dendrimer. At pH 11 the electrostatic repulsion between the negative charged forces the surface groups apart to

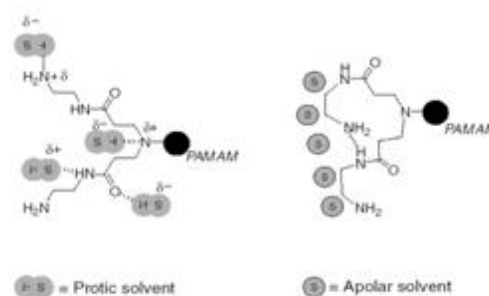
give a more extended conformation with a highly expanded surface area (Figure 12).



**Figure 11:** Two-dimensional depiction of conformational changes upon different pH of a carboxy-terminated PPI-dendrimer.

### 4.1.2 Effect of Solvent

The ability of the solvent to solvate the dendrimer structure is a very important parameter when investigating the conformational state of a dendrimer. Dendrimers of all generations generally experience a larger extent of back-folding with decreasing solvent quality, *i.e.* decreasing solvation. However, being more flexible, the low generation dendrimers show the highest tendency towards back-folding as a result of poor solvation compared to the higher generation dendrimers. NMR studies performed on PPI dendrimers conclude that a nonpolar solvent like benzene, poorly solvates the dendrons favouring intramolecular interactions between the dendrimer segments and back-folding. However, a weakly acidic solvent like chloroform can act as a hydrogen donor for the interior amines in a basic dendrimer like PPI, leading to an extended conformation of the dendrimer because of extensive hydrogen bonding between the solvent and the dendrimer amines.<sup>16</sup> Both experimental as well as theoretical studies on amino-terminated PPI and PAMAM dendrimers (polar dendrimers) show the tendency that nonpolar aprotic (poor) solvents induce higher molecular densities in the core region as a result of back-folding, whereas polar (good) solvents solvate the dendrimer arms and induce a higher molecular density on the dendrimer surface. Back-folding of the polar surface groups may expose the more hydrophobic dendrimer parts to the surroundings leading to a decreased surface polarity of the back-folded dendrimer.



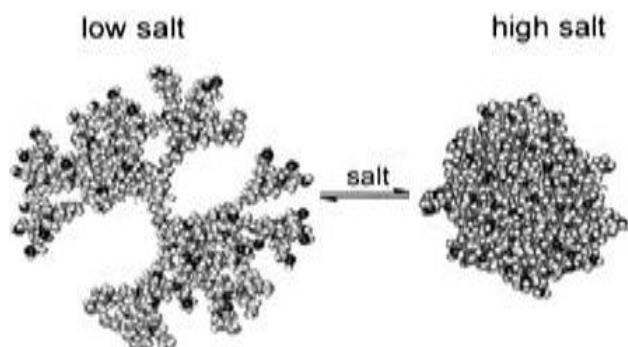
**Figure 12:** Proposed scheme for solvation of a dendrimer under different solvent conditions. (a) Solvation of a polar dendrimer in a protic solvent ("good") leading to extended conformation exposing a polar surface. (b) Solvation of a polar dendrimer in an



apolar aprotic solvent (“poor”) leading to exposure of an apolar surface consisting of alkyl chains by back-folding.

#### 4.1.3 Effect of Salt

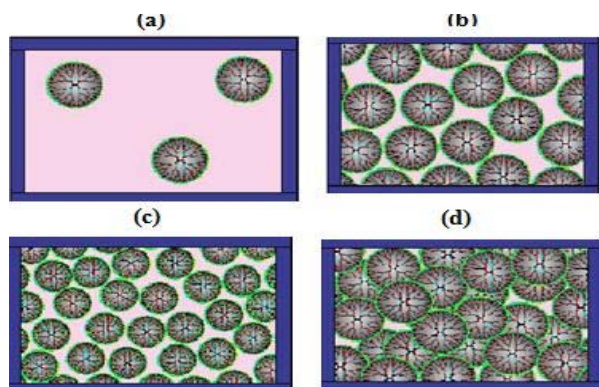
High ionic strength (high concentration of salts) has a strong effect on charged PPI dendrimers and favours a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor solvation. At low salt conditions, the repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure (Figure 14).



**Figure 13:** The three-dimensional conformational change of a PPI dendrimer upon increasing ionic strength

#### 4.1.4 Effect of Concentration

In dendrimers with flexible structures the conformation is not only affected 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 affect on the molecular density and conformation of the 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. 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.



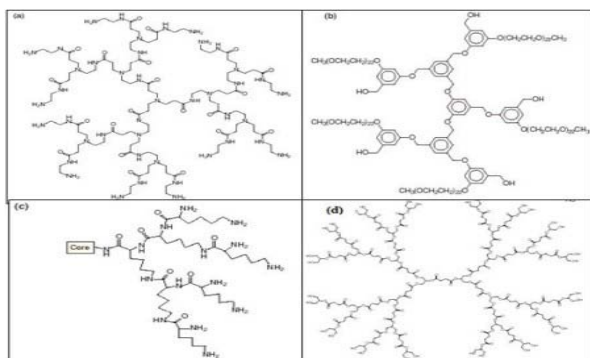
**Figure 14:** Dendrimer at different concentrations (a) Dilute (b) Contact (c) Collapse (d) Interpenetrate.

## 4.2 Biological Properties<sup>19-35</sup>

Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications. Size is a key determinant of dendrimer cytotoxicity for both PAMAM<sup>19</sup> and PPI dendrimers<sup>20</sup>. Cytotoxicity of PAMAM dendrimers increases with generation for both full generation cationic dendrimers (G2–G4) and the “half-generation” anionic intermediates (G2.5, G3.5)<sup>20-22</sup>. The nature and density of charged groups are other factors that determine dendrimer toxicity<sup>21</sup>. Cationic (surface) charges are in general more toxic but details depend on the specific groups involved, that is, for amines it has been proposed that primary amines are relatively more toxic than secondary or tertiary amines. A concentration dependent tendency to cause haemolysis and changes in erythrocyte morphology has been linked to the presence of  $-NH_2$  groups<sup>23</sup>. In contrast to PAMAM dendrimers PPI dendrimers with DAB and DAE cores did not show generation dependence for the haemolytic effect<sup>24, 25</sup>. Quaternisation has previously been used as a strategy to reduce toxicity of polymers<sup>26</sup>. The approach also seems to be beneficial for higher generation PPI dendrimers but for complexes the effects of quaternisation are complex and can include changes of complex morphology and physical chemistry, which are difficult to deconvolute<sup>23</sup>.

By contrast anionic dendrimers, e.g. those bearing a carboxylate surface, are not cytotoxic over a broad concentration range<sup>27, 28</sup>. So despite their broad applicability of commercially available polyamidoamine (PAMAM) dendrimers and Polypropyleneimine dendrimers (PPI), it is generally necessary to modify the surface amine groups of these dendrimers with neutral or anionic moieties to avoid the toxicity and liver accumulation associated with their polycationic surfaces<sup>23,30</sup>. Polyaryl ether dendrimers (Figure 16b), developed by Fréchet and Hawker<sup>31</sup>, have been tested for drug delivery applications, but their poor water solubility necessitates the extensive use of solubilizing groups at their periphery<sup>32, 33</sup>. In recent years, much effort has been devoted to the preparation of dendrimers that are designed to be highly biocompatible and water soluble. In addition, some dendrimers have been designed to be biodegradable, and monomer units that are chemical intermediates or products in metabolic pathways have been incorporated. For example, several peptide-based dendrimers, such as those based on polylysine (Figure 16c), have been reported, and have been developed as promising vaccine, antiviral and antibacterial candidates after suitable peripheral modifications. Fréchet and co-workers have recently prepared a dendritic analog of the highly biocompatible PEO as a promising backbone for biological applications. Various polyester dendrimers incorporating monomers such as glycerol, succinic acid, phenylalanine and lactic acid (Figure 16d) have been prepared by Grinstaff *et al.*, and their potential use in tissue engineering has been demonstrated. Dendritic polymers incorporating glycerol monomers have been

developed by Haag<sup>34</sup>. Several other dendrimer families, such as the amides synthesized by Schluter *et al.* and the triazines produced by Simanek *et al.*<sup>35</sup>, might also prove to be useful for biological applications.



**Figure 15:** Structures of biocompatible dendrimers that have been tested for drug delivery applications. (a) PAMAM dendrimer. (b) Polyaryl ether dendrimer. (c) Polylysine dendron. (d) Polyester dendrimer based on glycerol and succinic acid.

## 5. METHODS FOR CHARACTERIZATION OF DENDRITIC POLYMER<sup>14, 36</sup>

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

The development of mass spectroscopic techniques such as MALDI and electrospray mass spectrometry has allowed the absolute determination of dendrimer perfection. Mass spectrometric results on dendrimers demonstrate the extreme sensitivity of the technique and the uniformity of the molecular mass.

Scattering techniques measure the radius of gyration ( $R_g$ ) of dendrimers, which is an average of the spatial distribution of all of the units. Transmission electron microscopy (TEM) has been used to image individual dendritic molecules, usually the larger generations. Recently atomic force microscopy (AFM) has also been used to image dendritic molecules.

**Following methods can be used for characterization of dendritic polymers.**

- 1. Spectroscopy and spectrometry methods** like Nuclear Magnetic Resonance (NMR), Infra-red (IR) and Raman, Ultra-violet-visible (UV-VIS), Fluorescence, Chirality, Optical rotation, Circular dichroism (CD), X-ray diffraction, and Mass spectrometry.
- 2. Scattering techniques** like Small angle X-ray scattering (SAXS), Small angle neutron scattering (SANS), and Laser light scattering (LLS).

**3. Electrical techniques** like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis.

**4. Size exclusion chromatography (SEC).**

**5. Microscopy** like Transmission electron microscopy, scanning electron microscopy and atomic force microscopy.

**6. Rheology, physical properties** like intrinsic viscosity, Differential Scanning Calorimetry (DSC), and Dielectric spectroscopy (DS).

**7. Miscellaneous** like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc.

## Comparison of Characterization of Dendritically Branched Polymers by SANS, SAXS, and TEM

Small angle neutron scattering (SANS), small angle x-ray scattering (SAXS), and transmission electron microscopy (TEM) have been used to characterize the size, shape and interactions of dendrimers, hyper branched, and dendrigraft polymers. Size in terms of radius of gyration ( $R_g$ ) from scattering and diameter from microscopy can be routinely measured. Five technologically important factors of dendritically branched polymers have been identified and measured.

## 6. APPLICATIONS<sup>10, 13, 14, 28, 37-40</sup>

Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimers suitable for a variety of high technology uses and are as follows:

### 6.1 Pharmaceutical Application

#### 6.1.1 Dendrimers Drug Delivery: Targeted and Controlled Release Drug Delivery<sup>10, 14, 28</sup>

Dendrimers have attracted attention as possible drug carriers because of their unique properties namely their well defined three-dimensional structure, the availability of many functional surface groups, their low polydispersity and their ability to mimic. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug).

#### Delivery of Anticancer Drugs by Dendrimers and Dendritic Polymers<sup>10, 28</sup>

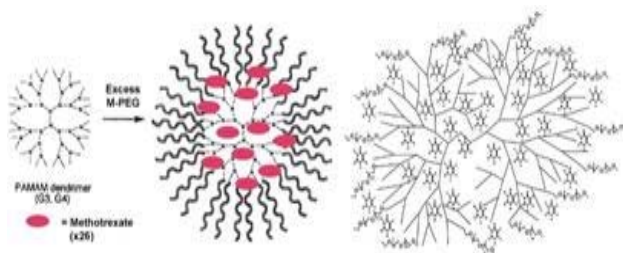
The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h). In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. Combined, these factors lead to the selective accumulation of macromolecules in tumor tissue – a





phenomenon termed the 'Enhanced Permeation and Retention' (EPR) effect<sup>28</sup>.

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. The encapsulation behavior of these compounds for the anticancer drugs adriamycin and methotrexate was studied. The highest encapsulation efficiency, with on average 6.5 adriamycin molecules and 26 methotrexate molecules per dendrimer, was found for the G = 4 PAMAM terminated with PEG2000 chains. The anticancer drug 5-fluorouracil encapsulated into G = 4 PAMAM dendrimers with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, and reduced release rate and hemolytic toxicity compared to the non-PEGylated dendrimer<sup>10</sup>. In contrast, up to 24 drug molecules were encapsulated into the hyper branched polyol. The drug was successfully transported into lung epithelial carcinoma cells by the dendrimers. Recent studies using Caco-2 cell lines have indicated that low generation PAMAM dendrimers cross cell membranes presumably through a combination of two processes, i.e., paracellular transport and adsorptive endocytosis, while cell efflux systems have a minor effect.



**Figure 16:** The encapsulation of anticancer drugs methotrexate (left) and 5-fluorouracil (right) into PEGylated generation 3 and 4 PAMAM dendrimers<sup>28</sup>.

### Mechanisms of Drug Delivery<sup>14, 28</sup>

Dendrimers are particularly attractive as they offer a high drug-loading capacity. 2 methods of dendrimer drug delivery are encapsulation of drugs and dendrimer –drug conjugates.

### Noncovalent Encapsulation of Drugs / Host –Guest Relation<sup>14, 28</sup>

Encapsulation of drugs uses the steric bulk of the exterior of the dendrimer or interactions between the dendrimer and drug to trap the drug inside the dendrimer. Maciejewski introduced the concept of encapsulating guest molecules into special, egg-shell-like structures<sup>14</sup>. Such a system can be used to encapsulate drugs and provide controlled delivery. Initial studies of dendrimers as potential delivery systems focused on their use as unimolecular micelles and 'dendritic boxes' for the noncovalent encapsulation of drug molecules<sup>14</sup>. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications, and

hydrophobic drugs and dye molecules were incorporated into various dendrimer cores. An advantage of using dendritic unimolecular micelles rather than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected. Although the introduction of stabilizing PEO chains on the dendrimer periphery has expanded the scope of dendritic unimolecular micelles to incorporate anticancer drugs such as 5-fluorouracil, methotrexate and doxorubicin and can slow the drug release rates in these systems to some extent<sup>14</sup>. A promising new approach to controlling the release of drugs from the encapsulating micellar compartment involves the use of hybrids of PEO and dendrimers with pH-sensitive hydrophobic acetyl groups on the dendrimer periphery<sup>14</sup>.

### Covalent Dendrimer–Drug Conjugates<sup>28</sup>

An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for the covalent attachment of drug molecules to the dendrimer periphery. In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer<sup>28</sup>. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids. The drug loading can be tuned by varying the generation number of the dendrimer, and release of the drug can be controlled by incorporating degradable linkages between the drug and dendrimer. Conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with non-specific toxicity and poor water solubility<sup>28</sup>. The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors. Furthermore, the dendrimer–platinum complex has been found to show increased efficacy relative to cisplatin in the treatment of subcutaneous B16F10 melanoma. By using a careful synthetic strategy with two different chain end functionalities, it is also possible to attach both hydrophobic model drugs and PEO moieties to the dendrimer periphery in a controlled manner<sup>28</sup>. Aliphatic polyester dendrimers based on 2,2-bis(hydroxymethyl) propionic acid are promising dendrimer backbones for the development of anticancer drug conjugates<sup>28</sup>.

### 6.1.2 Dendrimer As Solubility Enhancers<sup>28, 37</sup>

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers having a hydrophobic core and a hydrophilic surface layer have been termed unimolecular micelles. Unlike traditional micelles, dendrimers do not have a critical micelle concentration. This characteristic offers the opportunity to solubilize poorly soluble drugs by encapsulating them within the dendritic structure at all



concentrations of dendrimer. A hydrophilic–hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-fluorouracil, a water-soluble anti-tumor drug<sup>28</sup>. After phospholipid coating of the dendrimer–fatty- acid macromolecule, oral bioavailability in rats of 5-fluorouracil was nearly twice the level of free 5-fluorouracil. Dendrimer-based carriers could offer the opportunity to enhance the oral bioavailability of problematic drugs. Propranolol, conjugated to surface-modified G3 PAMAM dendrimer, the solubility of propranolol increased by over two orders of magnitude. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters<sup>37</sup>.

### 6.1.3 Cellular Delivery Using Dendrimer Carriers<sup>37</sup>

Kannan et al. studied the dynamics of cellular entry into A549 human lung epithelial carcinoma cells of a range of PAMAM dendrimers (G4-NH<sub>2</sub>, G3-NH<sub>2</sub>, G4-OH, PEGylated G3 [G3-PEG]) and a hyper branched polymer (polyol). G4-NH<sub>2</sub> and G4-OH entered cells more rapidly than did G3-NH<sub>2</sub>, polyol or G3-PEG. It was suggested that the rapid entry of G4-NH<sub>2</sub> 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-NH<sub>2</sub> compared with G4-NH<sub>2</sub> may be a result of fewer surface charges on the G3-NH<sub>2</sub> dendrimer<sup>37</sup>. 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 complexed drug inside cells. PAMAM dendrimers were surface-engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

### 6.1.4 Dendrimers as Nano-Drugs<sup>10</sup>

Poly(lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs)<sup>10</sup>. In earlier studies, it was found that PAMAM dendrimers covalently modified with naphthyl sulfonate residues on the surface, also exhibited antiviral activity against HIV. This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities. 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. Poly (lysine) dendrimers with mannosyl surface groups are effective inhibitors of the adhesion of *E. coli* to horse blood cells in a haemagglutination assay, making these structures promising antibacterial agents. Chitosan–dendrimer hybrids have been found to be

useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications.

### 6.1.5 Dendrimers in Photodynamic Therapy<sup>10, 28</sup>

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes. Photosensitive dyes have been incorporated into dendrimers and utilized in PDT devices<sup>10</sup>. This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue. The possibility of improving the properties of dendrimers through appropriate unfunctionalization of their periphery makes dendrimers promising carriers for photosensitizers. ALA is a natural precursor of the photosensitizer protoporphyrin IX (PIX), and its administration is known to increase cellular concentrations of PIX<sup>28</sup>.

### 6.1.6 Dendrimers in Gene Transfection<sup>10, 13</sup>

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<sup>10</sup>. A transfection reagent called SuperFect™ 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<sup>13</sup>. 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. It should be noted that dendrimers of high structural flexibility and partially degraded high-generation dendrimers (i.e., hyper branched architectures) appear to be better suited for certain gene delivery operations than intact high-generation symmetrical Dendrimers<sup>10</sup>.

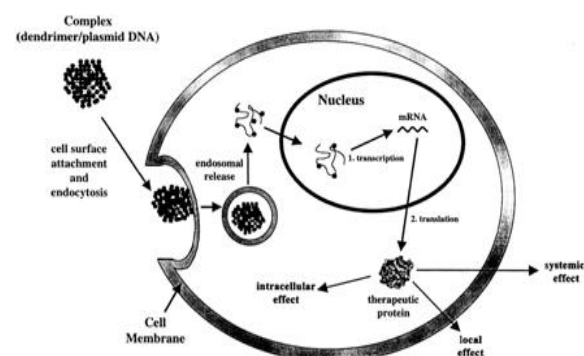


Figure 17: Dendrimer involved in gene transfection

**Table 2:** Various dendrimer based products

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

## 6.2 Non-Pharmaceutical Application

### 6.2.1 Diagnostics<sup>10, 38</sup>

Paramagnetic metal chelates such as Gd(III)- N,N',N'',N'''-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane (Gd(III)-DOTA), Gd(III)-diethylenetri- amine pentaacetic acid (Gd(III)-DTPA), and their derivatives used as contrast agents for magnetic resonance imaging (MRI)<sup>14</sup>. The (Gd(III)-DTPA) conjugate (MagnevistR) (Schering AG) and is a widely used MRI contrast agent. In another approach, the conjugation of (Gd (III)-DOTA) to poly (l-glutamic acid) (molecular weight 50 kDa) via the biodegradable disulfide spacer cystamine was studied to find a safe and effective macromolecular MRI contrast agent. Consequently, dendrimer-based Gd(III) chelates consisting of generations 2 and 6 PAMAM dendrimers with 12 and 192 terminal surface amines conjugated to the chelating ligand 2-(4-isothiocyanatobenzyl)-6- ethyldiethyle netriamine- pentaacetic acid through a thiourea linkage were synthesized. These contrast agents exhibited excellent MRI images of blood vessels upon intravenous injection. These dendrimer polychelates were exploited for high-quality MR angiography (MRA) images up to 60 min post injection. DNA-dendrimers, which are constructed for routine, use in high-throughput functional genomic analysis and as biosensors for the rapid diagnosis have genetic, and pathogenesis diseases<sup>10</sup>.

Radiolabelled monoclonal antibodies with high specific activity have been Prepared by attachment of PAMAM dendrimers loaded with<sup>111</sup> In or<sup>153</sup> Gd complexes In vivo oxygen imaging is a strategy that offers the potential for diagnosing complications from diabetes and peripheral vascular diseases, as well as the detection of tumors and the design of their therapeutic treatment<sup>10</sup>.

### 6.2.2 Dendritic Catalysts / Enzymes<sup>39, 40</sup>

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra filtration methods<sup>39</sup>. Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Because of their 'pseudo'-spherical nature and their resultant conformations the metal sites in these well-defined polymeric catalysts should be easily accessible for

substrate molecules and reagents, and therefore exhibit characteristics- fast kinetics, specificity and solubility<sup>40</sup>.

1. Metallo dendritic catalysts
2. Catalysis with phosphine-based dendrimers
3. Catalysis with (metallo) dendrimers containing chiral ligands
4. Non-metal containing dendrimers

### 6.2.3 Industrial Processes<sup>13</sup>

Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. Cooper and co-workers synthesized fluorinated dendrimers, which are soluble in supercritical CO<sub>2</sub> and can be used to extract strongly hydrophilic compounds from water into liquid CO<sub>2</sub><sup>13</sup>. This may help develop Technologies in which hazardous organic solvents are replaced by liquid CO<sub>2</sub><sup>13</sup>.

## 7. CONCLUSION

The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight, thereby offering new scaffolds for drug delivery. An increasingly large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

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