



## Dendrimer - An Emerging Approach for Drug Delivery

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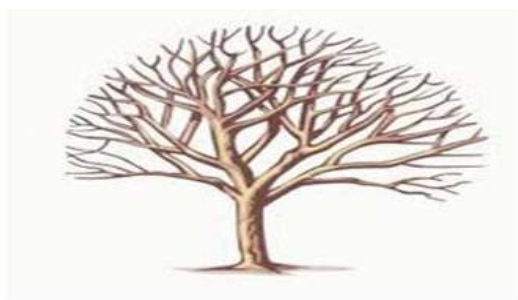
### ABSTRACT

An increasingly large number of drugs being developed today are facing problems of poor solubility, bioavailability and permeability. Controlling the release and targeting the drug to specific site for improving the therapeutic efficiency and minimizing the adverse effects of these drugs is an area of continuous research. In these formative years of nanotechnology dendrimers are considered to be a new class of polymerized macromolecules that carry a high potential for drug delivery. Considered as the polymer of 21<sup>st</sup> century dendrimer holds a promising future in various pharmaceutical and diagnostic applications because of its unique properties such as high degree of branching, multivalency, globular architecture and well defined molecular weight thereby offering scaffolds for drug delivery. Diversified applications can be obtained by controlling the architecture, shape, branching length, density and surface functionality of the dendrimers. The present review attempts to uncover all the aspects related to this novel and exciting class of highly branched three dimensional polymers. Dendrimer chemistry has attracted much attention for the past two decades because of their fascinating structural features. It is expected that future will witness an increasing number of commercialized dendrimer based drug delivery systems.

**Keywords:** Dendrimer, Drug delivery, Nanoparticulate.

### INTRODUCTION

**D**endrimer is a Greek word which means “part of the tree”. Dendron stands for “tree” and meros for “part”.

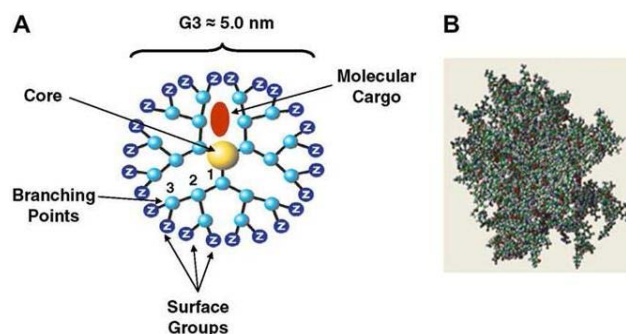


**Figure 1:** Branches of tree resembling dendritic structure

First discovered in early 1980's by Donald Tomalia and co-workers, dendrimer is generally defined as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers are made up by introducing the molecular groups on to the starting atom such as nitrogen. As the process repeats, successive layers are added and the sphere can be expanded to required size.

A dendrimer consists of;

- An initiative core
- Interior layer: also called as generation is composed of repeating units, radically attached to the initiative core
- Exterior layer: attached to the outermost interior generations.



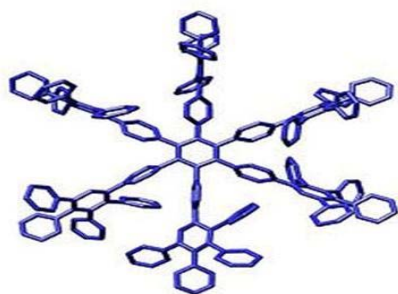
**Figure 2(A):** 2D representation of dendrimer demonstrating its different components **(B)** 3D representation of dendrimer.

### COMPONENTS OF THE DENDRIMER

#### Generation

It is the hyper branching 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 going from the core towards the dendrimer surface is the generation number. Dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer and abbreviated as 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 as generation “zero”, or in terminology as “G0”. The core structure thus presents no focal points as hydrogen substituent's are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted as half-generations; a

well-known example is the carboxylic acid-terminated PAMAM dendrimers.<sup>1</sup>



**Figure 3:** Crystal structure of a first-generation polyphenylene dendrimer<sup>2</sup>

### Shell

The dendrimer shell is the homostructural spatial segment between the focal points. 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.

### Pincer

In dendrimer, 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 dendrimer the number of pincers is half the number of surface groups (because in these dendrimers the chain divides into two in each focal point).

### 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”.

## TYPES OF DENDRIMER

### PPI dendrimer

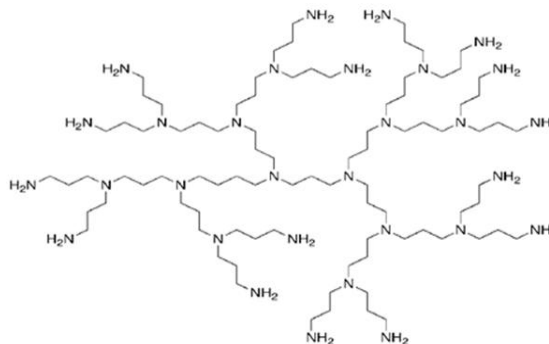
PPI stand for “Poly (Propylene Imine)” describing the propyl amine spacer moieties in the oldest known dendrimer type developed initially by Vögtle.<sup>3</sup> These dendrimers are generally poly-alkylamines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications now in the cancer therapy.

### PAMAM-dendrimers

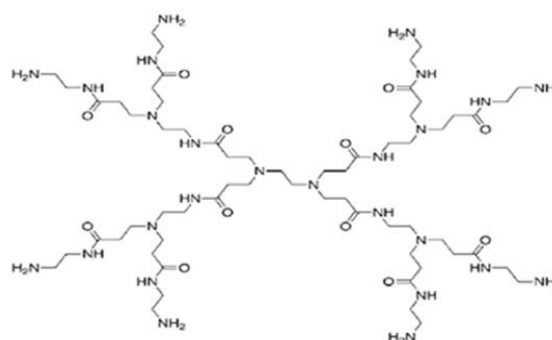
Polyamido-Amine (PAMAM), refers to one of the original dendrimer types built up by polyamide branches with tertiary amines as focal points. After the initial report by Tomalia and co-workers<sup>4</sup> in the mid-1980 PAMAM dendrimers, as PPI dendrimers are widely used in pharmaceutical science. PAMAM dendrimers are commercially available, usually as methanol solutions. The PAMAM dendrimers can be obtained having terminal or surface amino groups (full generations) or carboxylic

acid groups (half-generations). PAMAM dendrimers are commercially available up to generation 10.

*Starburst dendrimers* is a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethyleneimine core. The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions. These dendrimers are usually known under the abbreviation PAMAM (Starburst) or just Starburst.



**Figure 4:** Architect of PPI dendrimer



**Figure 5:** Architect of PAMAM dendrimer

### POPAM-dendrimers

POPAM [Poly (Propylene Amine)] closely resembles the PPI dendrimers. In addition, these dendrimers are also sometimes denoted “DAB-dendrimers” where DAB refers to the core structure which is usually based on Diaminobutane.

### PEI-dendrimers

It is a less common sub-class of PPI dendrimers based on Poly (Ethylene Imine) dendritic branches. The core structure in these dendrimers is diamino ethane or diamino propane.

### Fréchet-type dendrimer

It is a more recent type of dendrimer developed by Hawker and Fréchet<sup>5,6</sup> based on a poly-benzylether hyper branched skeleton. This type of dendrimer can be symmetric or built up asymmetrically consisting of 2 or 3 parts of segmental elements (dendrons). e.g. different generation or surface motif. 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.

### Multilingual Dendrimers

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

### Multiple Antigen Peptide Dendrimers (MAP-dendrimers)

MAP stand for "Multiple Antigen Peptide", 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 branching points. This type of dendrimer introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, e.g. vaccine and diagnostic research.

### 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 and reporting outcomes of therapy.

### Dendronized polymer

Dendronized polymers are linear to every repeated unit to which dendrons are attached. Dendrons are regularly branched, tree-like fragments and for larger ones the polymer backbone is wrapped to give sausage-like, cylindrical molecular objects. Figure 6 shows a representation with the backbone in dark grey and the dendrons like cake slices in light grey. It also provides a concrete chemical structure showing a polymethylmethacrylate (PMMA) backbone.

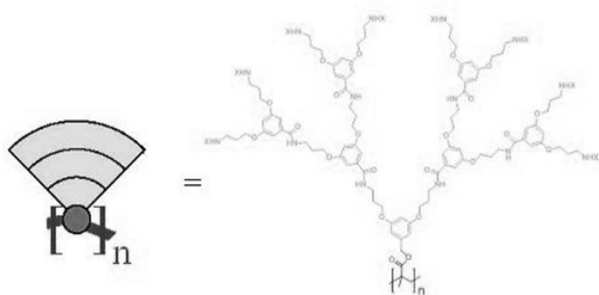


Figure 6: Dendronized polymer

### Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

### Metallo dendrimer

A Metallo dendrimer is a type of dendrimer with incorporated metal atoms. The metal can be situated in

the repeat unit, the core or at the extremities as end-group. Elements often encountered are palladium and platinum. These metals can form octahedral six-coordinate linking units from organic dihalides and the corresponding 4-coordinate monomers. Ferrocene-containing dendrimers and dendrimers with cobaltocene and arylchromiumtricarboxyl units have been reported in end-functional dendrimers. Metallo dendrimers can form metal complexes with dendritic counter ions for example by hydrolysis of ester terminated PAMAM dendrimers with sodium hydroxide.

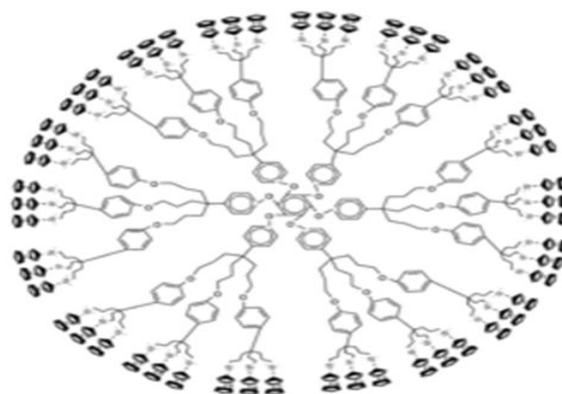


Figure 7: Ferrocene containing dendrimer

Metallo dendrimers are investigated as equivalents to nanoparticles. Applications can be expected in the fields of catalysis, as chemical sensors in molecular recognition - for example of bromine and chloride anions - or as materials capable of binding metals. Metallo dendrimers can also mimic certain biomolecules for example haemoprotein in dendrimer with a porphyrin core. Further uses are reported as electrocatalyst.<sup>7,8</sup> Examples of metallo dendrimer heterogeneous catalysis are a nickel-containing dendrimer active in the Kharasch addition, palladium-containing dendrimers active in ethylene polymerization and in the Heck reaction.<sup>9</sup>

### Synthesis of Dendrimer

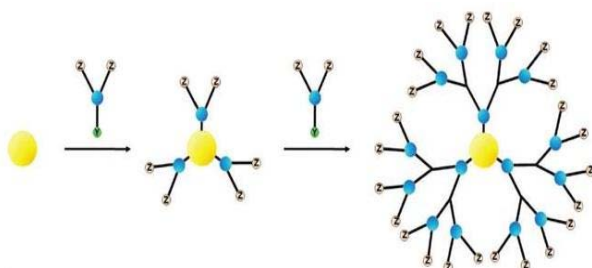
Presently dendrimers are commercially manufactured by companies like Dendritech (Midland, US), Dutch State Mines (DSM, Netherlands), Dow Chemical's (Michigan, US), Aldrich Chemical Company (Milwaukee, WI) and Weihai CY Dendrimer Technology (China). Following techniques are used for synthesis of dendrimers.

### Divergent Approach

Divergent approach comprises of two steps, first is the activation of functional surface groups, and second is the addition of branching monomer units.<sup>10</sup> In this approach, the core is reacted with two or more moles of reagent containing at least two protecting/branching sites, followed by removal of the protecting groups. This will lead to the formation of first generation dendrimer. This process is repeated several times until the dendrimer of the desired size is formed. PAMAM starburst dendrimers are prepared by this method.



As compared to other methods, divergent approach has some overriding advantages such as ability to modify the surface of dendrimer molecules by changing the end groups at the outermost layer. Another advantage is that the overall chemical and physical properties of dendrimer can be configured to specific need.<sup>11, 12</sup>

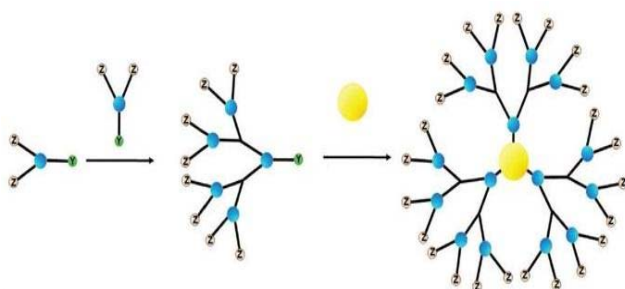


**Figure 8:** Divergent approach for synthesis of dendrimers

### Convergent Approach

This is an alternative method of dendrimer synthesis firstly proposed by Hawker and Frechet in 1990. Only one kind of functional group on the outermost generation is the main constraint of divergent growth method. Convergent growth would overcome such a weakness. Divergent method involves two stages, firstly iterative coupling of protected/deprotected branch to produce a focal point functionalized dendron; and secondly, divergent core anchoring step to produce various multi dendron dendrimers.

Precise control over molecular weight and production of dendrimers having functionalities in precise positions and number are some outstanding dividends of this method.<sup>5</sup> However difficulty to synthesize the dendrimer in large quantities, because of repeated reaction occurring during convergent approach that necessitates the protection of active site, is a significant limitation of both of these methods.



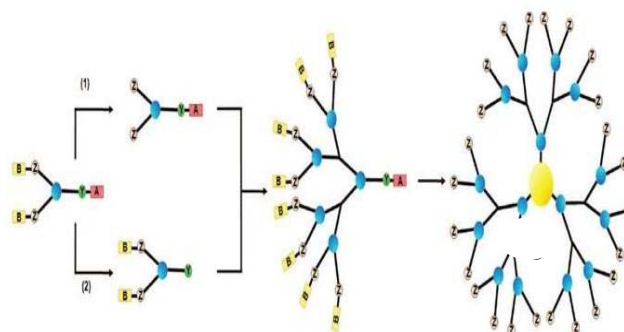
**Figure 9:** Convergent approach for synthesis of dendrimers

### Hypercores and Branched Monomers Technique

In this method oligomeric species are linked together to yield dendrimers in fewer steps and/or higher yields. Essentially a hypercore having multiple attaching groups is grown from core molecule and the surface units are linked to branched monomer with focal point activation leading to synthesis of blocks, which are then attached to hypercore to generate a higher generation dendrimers.

### Double Exponential Method

This approach allows the preparation of monomers for both divergent and convergent growth from a single starting material, which is similar to a rapid growth technique for linear polymer. The resultant two products are then reacted to give an orthogonally protected trimer, which can be used to repeat the growth again. Advantage of double exponential growth approach is rapid synthesis and applicability to either divergent or convergent method.



**Figure 10:** Double exponential method for synthesis of dendrimer

But this method has combined disadvantages of divergent/convergent methods like, higher generation dendrimers cannot be synthesized due to steric hindrance at the late stage, Increasing of protection/activation chemistry with generation requires highly efficient reaction scheme.

### Lego Chemistry Method

In order to simplify the synthetic procedure for dendrimers, in terms of cost as well as duration of synthesis, various approaches have been explored by scientists. Lego chemistry is one of the outcomes of these explorations. Lego chemistry is based on the application of highly functionalized cores and branched monomers and has been utilized in the synthesis of phosphorus dendrimers. The basic synthetic scheme has undergone several modifications and has resulted in a refined scheme wherein a single step can amplify the number of terminal surface groups from 48 to 250. Apart from higher growth in the number of terminal surface groups in few reactions, this method also encompasses the advantage of utilizing minimum volume of solvent, allowing simplified purification procedure with eco-friendly byproducts like water and nitrogen.<sup>13</sup>

## CHARACTERIZATION OF DENDRIMERS

### Spectroscopic Analysis

Many investigators have made use of functional probes in order to study dendritic microenvironments. These probes can either be attached covalently to the dendritic structure, like in the photochemical or chiral moieties, or they can be introduced as guest species. Spectroscopic methods have also produced information about dendritic microenvironments. PAMAM dendrimers have been

shown to have decreased  $^{13}\text{C}$  relaxation times for internal generations, suggesting that these moieties are less mobile than the surface groups. Rotational-Echo Double Resonance (REDOR) solid-state NMR spectroscopy has been used to examine the shape of the Fréchet polyethers, and Electron Spin Resonance (ESR) spectroscopy is used for examining complexed (PAMAMs) dendrimers. Computer modelling of dendrimers has been used extensively for the purposes of visualization and dynamics experiments.

### Thermal Analysis

Apart from spectroscopical methods, several thermal methods are also used in the characterization of dendrimers e.g. Thermogravimetric analysis, differential scanning calorimetry and isothermal titration calorimetry.

## APPLICATIONS OF DENDRIMERS

### In Cancer

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 effects of medications on healthy cells.<sup>14,15</sup>

Poly(amidoamine) (PAMAM) dendrimers are emerging as prospective candidates for efficient targeted drug and peptide delivery system due to their hyperbranched, well-defined globular nanometer-sized, multiple end modifiable groups and high biocompatibility.<sup>16,17</sup> PAMAM dendrimers have been used for drug delivery platform, by covalently conjugating drug molecules for cancer therapeutics. Conjugation of poor-bioavailable drugs with PAMAM dendrimer increases their bioavailability, and decreases dose frequency.<sup>18</sup> Methotrexate (MTX) conjugated with dendrimer showed 8-fold more toxic effect against resistant human acute lymphoblastoid, as compared to free MTX.<sup>19</sup> It has also been reported that tamoxifen conjugated to PAMAM dendrimer enhances the blood-brain barrier (BBB) transportation and improves the drug accumulation in glioma cells.<sup>20</sup>

The covalent attachment of drugs on to dendrimer surfaces offers stable dendrimer-drug conjugates. It is necessary to cleave the covalent attachment between drug and dendrimer in order to optimize drug release at the specific biological condition. The covalent linkage of the drugs to the surface functional groups of dendrimer can be achieved via ester or amide or disulphide bond, which can be cleaved hydrolytically or enzymatically or via glutathione.<sup>21</sup>

### For Gene Delivery

The ability to deliver pieces of DNA to required parts of a cell involves many challenges. Research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer-DNA complexes are encapsulated in a water

soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer-DNA complexes were used to encapsulate functional biodegradable polymer films for substrate mediated gene delivery. Research has shown that the fast degrading functional polymer has great potential for localized transfection.<sup>22</sup>

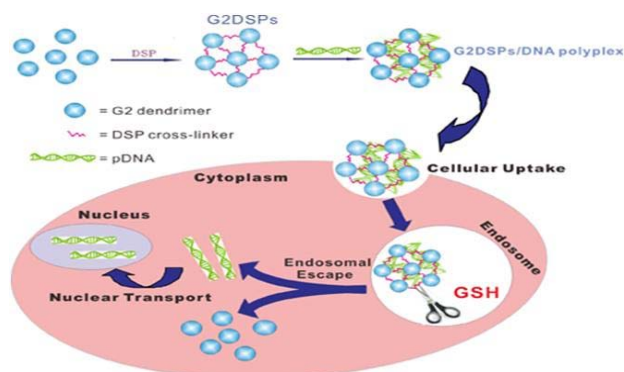


Figure 11: Gene delivery by dendrimer

### In Sensor Technology

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using cadmium-sulfide-polypropyleneimine tetrahexacontaamine dendrimer composites to detect fluorescence signal quenching,<sup>23</sup> and poly(propyleneamine) first and second generation dendrimers for metal cation photodetection<sup>24</sup> amongst others. Research in this field is vast and ongoing due to the potential for multiple detection and binding sites in dendritic structures.

### Blood Substitution

Dendrimers are also being investigated for use as blood substitutes. Their steric bulk surrounding a heme-mimetic centre significantly slows degradation compared to free heme<sup>25,26</sup> and prevents the cytotoxicity exhibited by free heme.

### For Nanoparticles Encapsulation

Dendrimers are also used in the synthesis of monodisperse metallic nanoparticles. Poly(amidoamide), or PAMAM, dendrimers are utilized for their tertiary amine groups at the branching points within the dendrimer. Metal ions are introduced to an aqueous dendrimer solution and the metal ions form a complex with the lone pair of electrons present at the tertiary amines. After complexation, the ions are reduced to their zerovalent states to form a nanoparticle that is encapsulated within the dendrimer.

### As Drug Carriers in Sexually Transmitted Diseases

Dendrimers as Nano-Drug carriers are useful against the herpes simplex virus as it can potentially prevent or reduce transmission of HIV and other sexually transmitted diseases (STDs), when drug delivery is made through Poly(lysine) dendrimers modified with sulfonated naphthyl groups.<sup>27</sup>

## For Drug Solubility Enhancement

Dendrimers have unimolecular micellar nature, due to hydrophilic exterior and hydrophobic interiors it forms covalent as well as non covalent complexes with drug molecules and hydrophobes and enhance its solubility behaviour.

### Dendrimer in Ocular Drug Delivery

PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in improving residence time and enhancing bioavailability of pilocarpine in the eye.<sup>28</sup>

### Dendrimers in Pulmonary Drug Delivery

Positively charged PAMAM dendrimers (G2 and G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.<sup>29</sup>

### Miscellaneous Applications of The Dendrimers

- Delivery of nucleic acids.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.

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.

### Drawbacks of The Dendrimers And Ways To Overcome

A serious drawback of dendrimers is their toxicity. However, this toxicity is mainly related to the positive charge present on the surface of the cationic dendrimers.<sup>30,31</sup> Appropriate modifications of the dendrimers surface can greatly reduce their toxicity.<sup>13</sup> Such modified dendrimers can be used in nanomedical applications, as they possess the advantage of dendrimers spatial structure and simultaneously possess reduced toxic activity.

To overcome the problem of toxicity the group of Michal Ciolkowski and Johannes F. Petersen have done surface modification of polyamidoamine (PAMAM) dendrimer of the fourth generation (G4). The amine surface groups of a G4 PAMAM-NH<sub>2</sub> dendrimer were transformed into pyrrolidone derivatives by means of reaction with dimethyl itaconate. The researchers reported reduced toxicity through interaction studies with human serum albumin (HSA), influence on viability of mouse neuroblastoma (N2a) cell line, as well as through hemolytic activity.<sup>21</sup>

### Future Prospect

Dendrimer drug delivery systems are very important and convenient for drugs and gene delivery. They provide a platform for the attachment of drugs or genes and their release through several mechanisms. Scientists have explored the use of dendrimers for various applications in

oral, transdermal, ophthalmic, and gene delivery. Although dendrimer drug delivery requires attention to certain manufacturing and biological considerations to be successful. Boosting of commercial applications of dendrimer technology will provide strength for its usefulness in future.

### Marketed Products of Dendrimers

**Table 1:** Name and use of marketed dendrimer products

Name of the product	Company	Utilization
Starburst	Dow chemical	Targeted diagnostic and therapeutic delivery for cancer.
Priostar	Starpharma	
Stratus CS	Dade Behring	Cardiac marker
Vivagel	Starpharma	Prevention of HIV infection
Alert ticket	US Army Research Lab.	Anthrax detection
SuperFect	Qiagen	Gene transfection
Taxotere	Sanofi Aventis	Anticancer drug delivery

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