## **Review Article**



# **DENDRIMER AND ITS APPLICATION**

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#### ABSTRACT

This article aims majorly on five areas namely: Basic concept, Types, Synthesis, properties & Applications of the dendrimer. Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behavior dendrimers are suitable for a wide range of biomedical and industrial applications. The unique architectural design of dendrimers, high degree of branching, multivalency, globular architecture and well-defined molecular weight, clearly distinguishes these structures as unique and optimum nanocarriers in medical applications such as drug delivery, gene transfection, tumor therapy, diagnostics, etc. The reflections on biomedical and industrial applications of dendrimers given in this report clearly demonstrate the potential of this new fourth major class of polymer architecture and indeed substantiate the high hopes for the future of dendrimers.

Keywords: Dendrimers, Gene, Therapy, Cancer tumor, Drug Delivery.

### INTRODUCTION

### **Basic Concept**

A strong demand on high quality polymeric products inclines the polymer scientists to produce their polymers with novel and innovative ideas.

Dendritic architecture is undoubtedly one of the most pervasive topologies observed universally throughout biological systems. These patterns are found at virtually all dimensional Length scales. They appear in many diverse prototypes including those that can be measured in meter, in circulatory topologies in the human anatomy that are found in mm and cm, or in cerebral neurons in  $\mu$ m.

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. He synthesized the first "**cascade molecules**".

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.

### Significance

Dendrimers are unique macromolecules and have a large number of significant features.<sup>1</sup>

• The Dendrimers are unique in structural features.

• They possess a large number of surface group and one type of functionality can be transformed to another by appropriate and simple method.

• Because of their unique structural features like no entanglement, high surface functionalities, they possess a wide variety of unusual properties, like low viscosity, high reactivity, higher solubility, interior cavity etc.

• The Dendrimers are monodisperse and hyper branched polymer which are the most important and unique feature for them.

• The surface becomes "dense packed" after a certain generation of growth and regular growth is stopped with incomplete functionalization of the terminal layer.

• They bring the active functional group in close proximity with easily accessible form.

### **Terms & Nomenclature in Dendrimer Chemistry**

Dendrimer chemistry, as other specialized research fields<sup>1,2</sup>, has its own terms and abbreviations. The evolution of three major macromolecular architecture, namely: linear (class I), cross-linked (bridged; class II) and branched types (class III). These three architectural classes are recognized as traditional synthetic polymers. In all these classes, structures or architectures are produced by largely statistical polymerization processes, rather than exact distribution processes (Fig. 1).

• **Dendrigrafts** are class of dendritic polymers like Dendrimers that can be constructed with a well-defined molecular structure, i.e. being monodisperse. However, in contrast to Dendrimers, Dendrigrafts are centered on a linear polymer chain, to which branches consisting of copolymer chains are attached. These copolymer chains are further modified with other copolymer chains and so on, giving a hyper branched motif built up by a finite number of combined polymers.

• **Dendrons** is the term used about a dendritic wedge without a core, the Dendrimer can be prepared from



assembling two or more Dendrons. As we shall see later, Dendrons are very useful tools in the synthesis of Dendrimers by the segment coupling strategy These Dendrons have been used in the creation of numerous of Dendrimers having different structures and functions.

• **Generation** is common for all Dendrimer designs and the hyper branching 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.

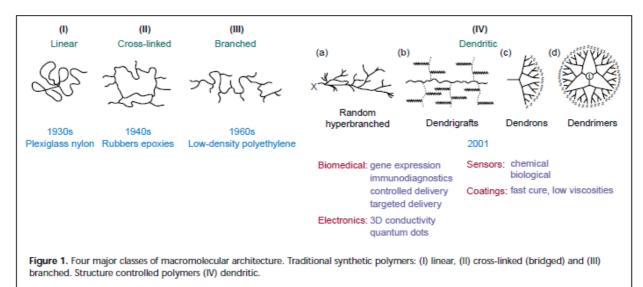
• **Shell**: The Dendrimer shell is the homo-structural spatial segment between the focal points, the "generation space". The "outer shell" is the space

between the last outer branching point and the surface. The "inner shells" are generally referred to as the Dendrimer interior.

• **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.

• **End-group** is also generally referred to as the "terminal group" or the "surface group" of the Dendrimer. The word surface group is slightly more inaccurate, in the sense that the Dendrimer branches can sometimes fold into the interior of the Dendrimer. Dendrimers having amine end-groups are termed "amino-terminated Dendrimers".



### STRUCTURE

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.<sup>2,3</sup> 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.

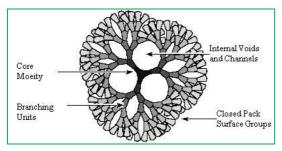


Figure 2: The Dendritic Structure

Dendrimers possess three distinguished architectural components, 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.

### **SYNTHESIS**

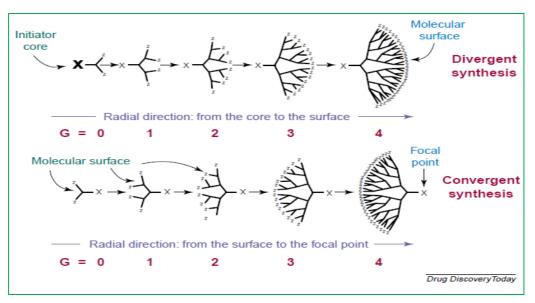
# Synthetic methodology

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. 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.<sup>1-</sup>

(1) **Divergent Method**: In which growth of a Dendron (molecular tree) originates from a core site (Fig. 3). During



the 1980s, virtually all dendritic polymers were produced by construction from the root of the molecular tree. This approach involved assembling monomerric modules in a radial, branch-upon-branch motif according to certain dendritic rules and principles. This divergent approach is currently the preferred commercial route used by worldwide producers including Dendrimax (AnnArbor, MI, USA), DSM Fine Chemicals (Geleen, The Netherlands) and The Perstorp Group (Perstorp, Sweden). (2) Convergent Method: A second method that was pioneered by Fréchet and colleagues is the convergent growth process. It proceeds from what will become the Dendron molecular surface (i.e. from the leaves of the molecular tree) inward to a reactive focal point at the root (Fig. 3). This leads to the formation of a single reactive Dendron. To obtain a Dendrimer structure, several Dendrons are reacted with a multi-functional core to yield such a product.



**Figure 3:** 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.

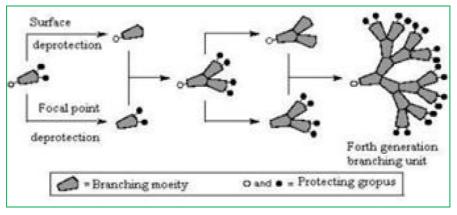


Figure 4: Double Exponential and Mixed Growth

(3) Accelerated Approach: The divergent and convergent methods are largely used to synthesize various Dendrimers successfully, but both are suffering from common problem of multistep and laborious procedures. So they are time consuming processes, and overall low yield makes the macromolecules more expensive. Recently thus accelerated approaches are being used for the synthesis of Dendrimers. These are Double Exponential and Hyper core techniques. The common feature of both is to reduce the number of steps for the synthesis of Dendrimer drastically. This greatly

accelerates the synthetic process and thereby decreases the work load and ultimately the cost of the polymer.

a) Hyper core and Branched monomer: The approach involves the pre-assembly of oligomers, which can be then be linked together to offer the desired Dendrimer by a few steps with overall good yield. This approach is more like a convergent approach with less number of steps requirement for the generation of Dendrimers.

**Double exponential & 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. These two products are reacted together to give an orthogonally protected trimmers, 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.

# PHARMACEUTICAL APPLICATION

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

# Delivery of Anticancer Drugs by Dendrimers and Dendritic $\mbox{Polymers}^5$

Cancer is a killer disease second only to heart problems. Though there is significant progress in the field of anticancer technology, we are still badly in need of a reliable cure for malignant growths. At present, a variety of drug delivery approaches including polymer microcapsules and microspheres microspheres, liposomes, polymer conjugates, and nanoparticles are either FDA-approved or are in clinical development as cancer treatments. During the last few decades in particular, medical science has witnessed the exploration of several delivery devices and along with them a multitalented versatile star named "dendrimers" is now visible on the horizon. Dendrimers are synthetic macromolecules with a tree-like well-defined branched structure. Their peculiar architecture and flexibility in modifying it in numerous ways has been an active area of research. Since their introduction the unique characteristics of dendrimers have led to an exponential increase in the number of publications in this innovative field. Recently, progress has been made in the application of biocompatible dendrimers to cancer treatment, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin. (Figure 5)

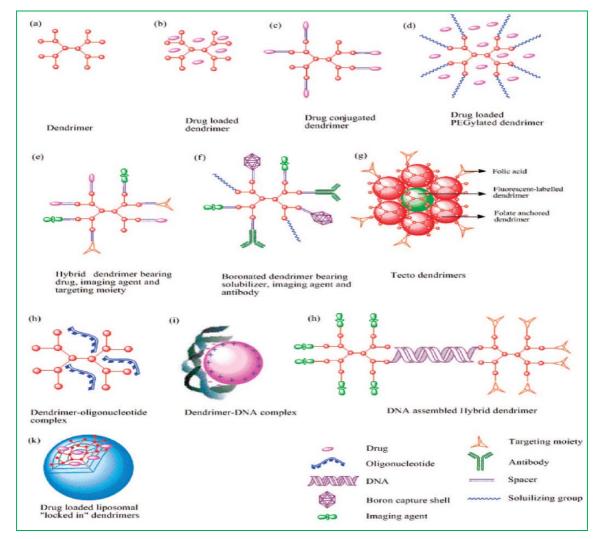
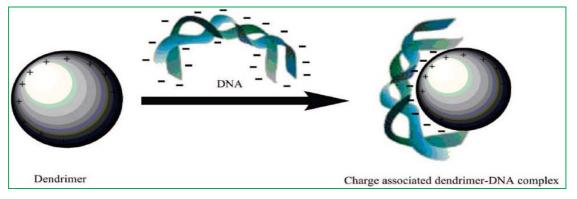


Figure 5: Schematic diagram showing different dendritic conjugates employed to date in cancer therapy and diagnosis.





**Figure 6:** Schematic diagram showing formation of dendrimer-DNA complex mediating charge interaction between positively charged dendrimer and negatively charged DNA

### Dendrimers in Gene Transfection:<sup>6,7,8</sup>

Gene therapy focuses on the correction of genetic defects by transferring active genes into target cells. The key to success in gene therapy specifically relies on exact a deficient delivery of genetic material to target cell populations. An ideal therapeutic DNA delivery vector would possess a high degree of target cell specificity, high transfection efficiency, easy biodegradability, good stability, and a near baseline potential for the occurrence of toxicity and immunogenecity. In addition, it should be simple to design and synthesize DNA release and expression. A number of delivery devices such as polyethylenimine (PEI) and chitosans have been designed as carriers for DNA molecules with these goals in mind. Viruses were the earliest gene delivery vectors, but the risks associated with them limit their carrying ability, especially since they can be strongly immunogenic because of their proteinaceous capsid. Such toxicities have been seen in numerous animal models.

At about the time of Seib's studies, dendrimer-DNA complexes formed as a result of ionic interaction between positively charged dendrimer and negatively charged DNA fragment came into use to transport DNA (Figure 6).

Magnetic nanoparticles (MNP) with a diameter of 8 nm modified with different generations were of polyamidoamine (PAMAM) dendrimers and mixed with antisense surviving oligodeoxynucleotide (asODN). The MNP then formed as ODNdendrimer-MNP composites, which we incubated with human tumor cell lines such as human breast cancer and liver cancer and then analyzed by 2,5-diphenyltetrazolium bromide, guantitative reverse transcription-PCR, Western blotting, laser confocal microscopy, and high-resolution transmission electron microscopy. Results showed that the as ODN-dendrimer-MNP composites were successfully synthesized, can enter into tumor cells within 15 min, caused marked downregulation of the survivin gene and protein, and inhibited cell growth in dose-and time-dependent means. No.5 generation of as ODN-dendrimer-MNP composites exhibits the highest efficiency for cellular transfection and inhibition. These results show that PAMAM dendrimermodified MNPs may be a good gene delivery system and have potential applications in cancer therapy and

molecular imaging diagnosis. PAMAM dendrimers are a class of polycationic synthetic polymers that can be used for gene transfer.

There are some reports which suggest that lower generations also can be effective in gene delivery. DeLong et al. showed that a 3.0G PAMAM endrimer forms stable complexes with oligonucleotides. The 1:1 and 20:1 complexes of dendrimer and ligonucleotide significantly increased the cellular uptake by about 3-4 and 50 folds, respectively. These results were in contrast to those of Tomalia and co-workers, who reported that efficient complexation and facilitated cellular uptake of DNA occurred only when higher generation PAMAM dendrimers were used. PAMAM dendrimers have now been established as an efficient class of polycationic synthetic polymers used for gene transfer. The 3dimensional spherical structure of dendrimers offers control of the molecule in terms of generation and degree of branching. This control can produce polymer particles with a very low degree of polydispersity, which is a striking advantage over other classes of polymers such as PLL that generate extremely polydisperse particles. It is noteworthy that low polydispersity can lead to reproducible gene delivery and a clinically reliable formulation.

### Dendrimer in Drug Delivery<sup>9</sup>

Dendrimers have attracted attention as possible drug carriers because of their unique properties: their well defined three-dimensional structure, the availability of many functional surface groups, their low polydispersity and their ability to mimic biological molecules such as proteins and lipids. There have been numerous reports on the interactions between drugs and dendrimers, and the properties of such systems; however, it is only recently that dendrimers have been investigated as drug carriers in order to overcome cellular barriers.

Since their introduction some 30 years ago, supramolecular (self-assembling) vectors, such as liposomes, have had isolated successes in drug delivery applications; for example, DaumpXome<sup>®</sup> (Nexstar Pharmaceuticals, Boulder, CO, USA) and Doxil<sup>®</sup> (Sequus Pharmaceuticals, Menlo Park, CA, USA).



Recently, there appears to be a significant renaissance in the macromolecular drug delivery field this revolutionary concept was first introduced by Ringsdorf in the mid-1970s.More recent work by Fréchet and colleagues and Duncan and coworkers69 has highlighted the unique drug-loading capabilities and targeting features offered by dendrimers. Recent work has confirmed earlier reports that PAMAM dendrimers develop predictable nanoscale container and nanoscale surface-scaffolding properties. Unique periodic properties develop as a function of generation enhancement and are a consequence of mathematically defined surface-group amplification.

Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids. 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. The release of drug from such a prodrug occurs via chemical or enzymatic cleavage of a labile bond. The covalent linkage of a drug to a dendrimer provides a stable system that is not dependent upon the physical or thermodynamic factors which apply to encapsulated Several groups have investigated systems. the conjugation of drugs to PAMAM dendrimers as drug delivery systems. For example, 5-fluorouracil-PAMAM dendrimer conjugates (G4 and G5) gave a slow release of 5-fluorouracil, whereas 5-aminosalicylic acid was conjugated using two different spacers to a G3 PAMAM dendrimer for use as a carrier for colonic delivery.

# Use of dendrimers to cross cellular barriers: <sup>9</sup>

It has been demonstrated that dendrimers can cross cell barriers such as epithelial cells in the gastrointestinal tract, providing the opportunity for oral delivery using dendrimer-based carriers Tajarobi et al investigated the transport of fluorescently labeled cationic PAMAM dendrimer generations (G0-G4) across Madin-Darby canine kidney cells. The rank order of dendrimer permeability was of G4\_ G1 \_G0 > G3 > G2, and it was concluded that transepithelial transport was both a function of dendrimer size and interaction with the cells. Transport studies of PAMAM dendrimers across Caco-2 cell monolayers revealed that cationic dendrimers decrease transepithelial electrical resistance and increase the permeability of the paracellular marker mannitol at concentrations that were shown to be non-toxic to cells, suggesting that PAMAM dendrimers modulate the tight junction between Caco-2 cells.

Several studies have shown, using Caco-2 cells, that the permeability and cytotoxicity of PAMAM dendrimers is a function of size, surface charge, surface group, molecular weight and concentration of dendrimer.

# 3.5 Dendritic medical imaging systems <sup>10,11</sup>

Medical imaging is now a well-established field that encompasses techniques ranging from X-ray scanning to newer methods, such as MRI. Improvements in this field have been achieved by the utilisation of pigments, dyes and contrast agents. The need for aqueous soluble pigments, dyes or contrast agents in these techniques makes dendrimers a natural choice for use in their formulation.

Dendrimers have been tested in preclinical studies as **contrast agents** for magnetic resonance. Placing a patient in a generated, defined, inhomogeneous magnetic field results in the nuclear resonance signal of water, which is assigned to its place of origin and converted into pictures. Addition of contrast agents (paramagnetic metal cations) improves sensitivity and specificity of the method.

An MRI system images the body in a manner similar to that employed by a conventional nuclear magnetic resonance (NMR) spectrometer when analysing organic compounds. The variety of tissues and organs in the body feature different water contents and thus exhibit differential responses and can be distinguished from one another using MRI. The water content differences between tissues and, in particular, between normal tissue and tumours, are not significant and visualising tumours has thus proved difficult. Consequently, contrast agents that are incorporated selectively into tumours, and thus serve to increase visibility of these uncontrolled growths, are desirable.

# Dendrimers In Photodynamic Therapy: <sup>12,13</sup>

Photodynamic therapy (PDT) is a nonthermal technique for inducing tissue damage with light following administration of a light-activated photosensitizing drug which can be selectively retained in malignant or diseased lesions relative to normal adjacent tissue. Activation of the photosensitizer results in the generation of reactive oxygen species (ROS), mainly singlet oxygen via interaction of the sensitizer triplet state with molecular oxygen. The ROS oxidize intracellular substrates such as lipids and amino acid residues leading to cell death.

The most widely studied application of PDT to date is in cancer therapy. However, using conventional exogenous sensitizers, skin photosensitivity can be prolonged, and damage to normal tissue is rarely avoidable due to poor tumor selectivity. The use of 5-aminolevulinic acid (ALA) is a relatively new approach in PDT. ALA is a natural precursor of protoporphyrin IX (PpIX), an effective photosensitizer, and cellular concentrations of PpIX can be increased by the administration of 5-aminolevulinic acid (ALA).

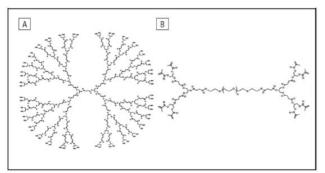
A certain amount of tumor selectivity can be achieved since porphobilinogen deaminase activity is increased and ferrochelatase (the enzyme which catalyzes the conversion of photoactive PpIX into inactive heme) levels are decreased in tumor cells. For therapeutic applications, PpIX is activated using red light (typically at 635 nm), with mitochondria believed to be key targets of singlet oxygen oxidative damage resulting in cell death mainly via apoptosis. PpIX levels return to normal after 24 h, following administration so skin photosensitization is relatively short-lived compared to many exogenous



sensitizers. A major limitation of ALA-PDT is the low intracellular availability of ALA. Cellular uptake of ALA occurs via a relatively slow active transport mechanism.

# New Dendritic Adhesives for Sutureless Ophthalmic Surgical Procedures:<sup>14</sup>

In human patients, corneal perforations are repaired with sutures. However, the use of sutures has limitations and drawbacks. First, suture placement itself inflicts trauma to corneal tissues, especially when multiple passes are necessary. Second, sutures such as 10-0 nylon are not without problems. Suture material may incite infection, inflammation, and vascularization; corneal scarring is more prone to develop with inflammation and vascularization present. Third, because of uneven tension on the sutures, asymmetric healing and irregular astigmatism may arise. The postoperative integrity of the sutures may also be problematic, with suture loosening or breaking requiring timely removal. Last, a prolonged operative time and technical skill are needed for effective suture placement. Dendrimers offer innovative solutions to address tissue engineering challenges such as the design of novel tissue adhesives. Unlike linear polymers, like cyanoacrylate or hyaluronic acid, dendrimers are composed of a specific number of branched repeat units that emanate from a central core (Figure 7). The highly branched framework provides many peripheral functional groups that can be modified based on the desired application. In fact, through the proper selection of core and branched repeat composition and number of branched repeat units, dendrimers can be tailored for specific applications.





# Dendrimer as Solubility Enhancers:<sup>15</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 soluble 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-flurouracil, a water-soluble anti-tumor drug. After phospholipid coating of the dendrimer–fatty-acid macromolecule, oral bioavailability in rats of 5-flurouracil was nearly twice the level of free 5-flurouracil. Dendrimer-based carriers could offer the opportunity to enhance the oral bioavailability of problematic drugs. Propranolol, conjugated to surfacemodified 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.

## CONCLUSION

The dendritic polymers are considered as the 21<sup>st</sup> highly branched novel century's and useful macromolecules. 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. The chemical modification of the dendritic polymers resulted in a wide range of variation in properties, hence their application.

In order to realize their full potential, the simple methodology for synthesis need to be developed which allows faster and mass cycle synthesis to a level of an industrial acceptance. As the number of available dendritic polymers expands, their potential applications are also explored. However, to get the maximum benefits of the novel class macromolecules, a research by collaboration is very much essential. Finally it is one of the youngest and exciting fields of polymers researches where all branches of science can take part and hence, deserves more intensive attention.

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