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Dendrimers as smart materials for developing the various applications in the field of biomedical sciences

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ABSTRACT

Developing new smart materials and tracking their structural potential have been in focus for curing disease and other applications such as catalyzing biomolecules like proteins and selective bioremediation of toxic metals, dyes, pesticides have been thrust areas of research in the field of materials and biomaterials sciences. Since materials are most important need of the society which develops somewhere food, drug, fuel, protective cover, defense materials, fire resistant and acoustic mechanism, UV sensitive, UV absorbing, solar radiation trapping activities. In this context, the dendrimers have been considered as ideal and smart materials to be applied for wider applications and directly, indirectly or catalyze modulator and many others. Thus, the dendrimers act as smart materials and the synthesis of such architectural and potential molecules is being considered as a new thrust area for multitasking materials with better activities to catalyze chemical and biochemical processes. The multifunctional materials of multipurpose uses with several dendrimeric branching, having innumerable binding sites and are in high demands for their drug binding, loading potential and bio coatings. Copyright © 2016 VBRI Press.

Keywords: Dendrimers; smart materials; biochemical applications; biomedical applications.

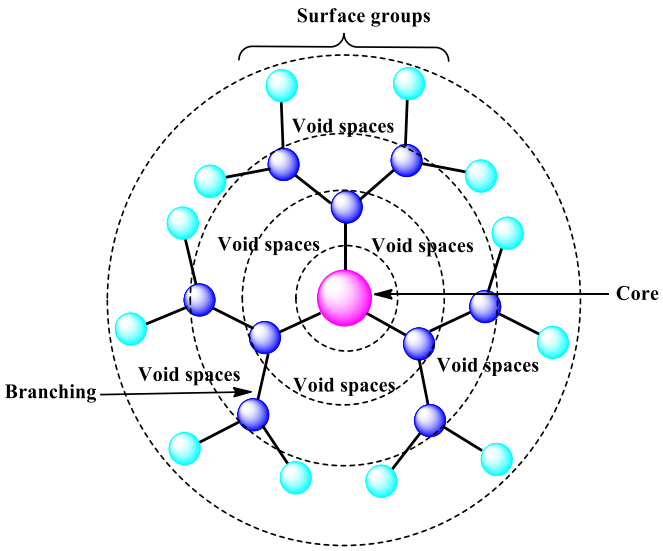


Fig. 1. General structure of dendrimer.

Introduction

The terminology 'dendrimers' originated from the Greek nomenclature, emanating from two words, viz. 'dendron', meaning tree and 'meros' that signifies a part or a sense of belonging. Essentially, dendrimers signify the giant molecules which have an intensively branched 3-dimensional (3D) structure, monodispersed character and are structurally polyvalent with precisely defined molecular structures. Several other terminologies also prevail with the help of which dendrimers are known in the scientific world such as cascade molecules, arborols and cauliflower with dynamic and highly useful building units because of their unique structure and properties **[1-6].** Two essential features of dendrimers that are frequent with other similar naturally occurring systems are their globular structure and polyvalent character. Besides this, these molecules possess monodispersity and highly branched 3D architecture which makes their structural engineering easy and impart those extraordinary functionalities **[7-8]** as shown in **Fig. 1.** Due to these features, dendrimers have been increasingly employed for structural tagging and biosynthetic applications by imparting them a biocompatible morphology. This is also evident from

their practically proven applications in the biomedical domain.

Interestingly, the synthetic organic chemistry witnessed the unveiling of cascade molecules as dendritic structures for the first time through the efforts of Vogtleand co-workers **[9]**. The gradual introduction of advanced synthetic methods led to the formation of larger dendritic assemblies was obtained and named as dendrimers.

The first ever discovered the dendritic structure was reported by Denkewalter *et al*. in 1981 **[10]**. The dawn of 1980's saw the immensely deep inroads being built to study and synthesis of dendrimers through the publication of original works conducted by Vogtle **[11]**, Tomalia **[12]** and Newkome **[13]**, through which the contribution of different research groups regarding the development of synthetic methodologies and efforts to employ dendrimers for specific applications came to the forefront **[3, 13]**.

One of the eye catching features of dendrimers is the possibility of numerous functional entities on the surface presenting larger scope for functionalization and engineering with numerous applications **[14, 15]**. These attributes are vitally responsible for the numerous applicability of dendrimers in the vast domains such as catalysis **[16],** chirality recognition **[17]**, formation of unimolecular micellar networks **[18]**, analysis of host-guest chemistry **[19]**, optimization of light harvesting **[20-22]** and synthesis of liquid crystalline materials **[23-30]**. The polymeric nature of dendrimers makes it a highly enriched feature by optimizing the repeated units in the structure into functionally diverse assemblies.

The diversity is suited particularly to their large scale synthetic applications as the repeating units ranging from pure hydrocarbons to peptides and sometimes even the coordination compounds. The two most commonly used dendrimers are composed of poly (amidoamine) (PAMAM) **[12]** and poly (propyleneimine) (PPI) functionalities. These have been produced at the industrial scale and are routinely used for commercial purposes as well; the research work focuses on the divergently synthesized PPI dendrimers, which have been independently reported by Mulhaput **[31]** and De Brabander **[32]**. Dendritic structures are quite commonly observed in nature. The hyperbranched structures of these molecules impart them the advantage of displaying a particular characteristic motif in multivalent manner, which is the prime factor responsible to impart synergistic enhancements of the characteristic functions.

Of late, in an interesting revelation, a scientific report on the dry adhesion of Geckos feet to surfaces has pointed out that this foot is constituted by a dendritic network of hairs which ultimately results in the establishment of millions of foot hairs. These foot hairs are responsible for the genesis of extraordinary strong adhesive forces which also include van der Waal forces that act locally between each foot hair and the corresponding surface. Surprisingly, despite the large molecular size, dendrimers are structurally well-defined with comparatively lower polydispersity as compared to traditional polymers. On a molecular level, the dendritic branching in these giant molecules results in semi-globular to globular structures. A vital feature of all these structures is the presence of high functionality on the surface despite of having a small molecular volume.

Due to globular texture, the dendrimers with larger generation, occupy a smaller hydrodynamic volume when compared to corresponding linear polymers. Interestingly, in comparison of globular proteins, dendrimers have a larger hydrodynamic volume. The dendritic structure of dendrimers is mainly characterized by the presence of layers that are present between each focal point (or cascade). The number of these layers is frequently defined as the generation or functionality of a dendrimer. For illustration, a G5 dendrimer has 5 cascade points when we move from core towards the surface. The numeric terminology used for core is zero as there are no cascades points present in it. For instance, in case of PPI dendrimer, the core is 1,4-diaminobutane which possesses no cascade points; whereas in a PAMAM dendrimer, the core is constituted of ammonia and related moieties. Importantly, in PAMAM hydrogen substituents are not considered as focal points **[31-33]**. In PAMAM dendrimers, the intermediary molecules bearing carboxylate groups on the surface are designated as half generation (G1.5 or G2.5) dendrimers.

The designing of dendrimers is synergically based that is composed of a large variety of branching, such as polyamines in PPI dendrimers **[9]**, a mixture of polyamides and amines in PAMAM dendrimers **[33]** or built up by several hydrophobic aryl ether subunits that prevail in a polymeric form **[34]**. Some of the very recent configurations of dendrimer design are based on carbohydrate **[35]**, calixrane subunit core structures **[36]** and third period elements such as silicon and phosphorous **[37]**. Due to a great deal of structural and synthesis based approaches being employed to create these multifunctional structures, PAMAM and PPI dendrimers have been extensively employed for biomedical applications that are based on their specific and localized interactions with the biological systems.

Physicochemical properties of dendrimers

Interesting applications of dendrimers stem are found from the literature that with the addition of each additional functional unit, the structural components of the dendritic structure begin to show the characteristic features that are more intensively expressed with every successive increase in a generation. Overall, a typical dendrimer structure can be assumed to be consisting of three units, namely:

(i) A multivalent surface with a structural provision of multiple chemical moieties tagging and thereby imparting high functionality to the overall molecule. Sometimes the surface of a dendrimer molecule can act as a shielding layer for the dendrimer molecule from the chemical fluctuations taking place in the vicinity. As a consequence of this phenomenon, sometimes the molecule gets extensively closer and it further affects the diffusion of several useful solvent molecules into the dendrimer interior.

(ii) The outer shell, which has a very specific environment, ensured in part by its shielding from the surroundings through the dendrimer surface. These are the characteristic large number of functionalities

prevalent on the dendrimer surface as well as the outer shell which makes this molecule highly suitable for a range of diverse host-guest interactions and catalysis, where a close structural proximity of the enclosed functional motifs is very essential.

(iii) The core, which is the innermost region in a dendrimer molecule. As the dendrimer generation increases the tendency of getting shielded from the surroundings by the dendritic wedges also increases. This leads to the creation of specific localized surroundings within a dendrimer molecule that is significantly different from the one in outer vicinity. For instance, water soluble dendrimers with non-polar moieties in the interior have been engineered to carry hydrophobic drugs into bloodstream **[38]**. The identity of the distinct three units of a dendrimer molecule can be manipulated with respect to accomplish with the design and usage for particular applications such as diverse as drug delivery, molecular sensors, enzyme mimicking and many others. A careful glance at the molecular size and physicochemical properties of the dendrimers reflects that the molecular size limits of a higher generation dendrimer are comparable with that of the medium sized protein molecules **[39]**. It is due to this that very early in history of dendrimer exploration, it was being speculated that these are the nanoscale polymers that can be used as building blocks of synthetic proteins via biological mimicking **[40]**. A differentiating feature of such dendrimer structure is the presence of a large number of multifunctional groups on the surface as compare to proteins of similar size. It can be well judged from the fact that the weight of a G6-PAMAM dendrimer is almost only half that of protein (ovalbumin) with comparable molecular size.

This is primarily due to the fact that a dendrimer has a lower molecular density, which in turn is due to its low molecular density (even lower than a protein). On the other hand, in a protein, the higher molecular density is due to the tightly folding of a linear polypeptide chain into a characteristic three dimensional structure through extensive intermolecular ion-pairing, hydrogen and hydrophobic bonding and disulphide cross binding **[41]**. On the other hand, when compared with linear polymers, the dendrimers are generally more compact molecules that occupy a smaller hydrodynamic volume **[42]**. Consistent and rigorous investigations of supramolecular dendrimer aggregates have revealed that as the generation or the functionalization order of a typical dendrimer is increased it shows a tendency to become increasingly globular in shape (particularly more spherical in contrast to being linear) so as to make possible the spreading of larger molecular structure with a minimized repulsive interaction between the constitutive segments **[43]**.

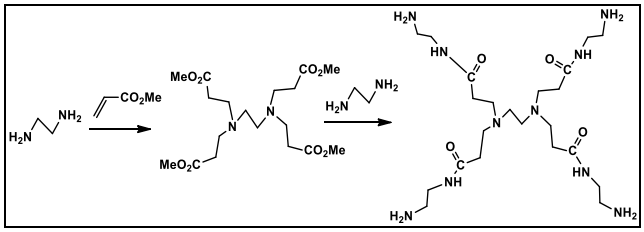
Biologically and biochemically active dendrimers

A dendrimer possesses several useful chemicals and physical attributes that can be specifically optimized by changing the corresponding monomeric unit involved. In a typical dendrimer molecule, there exist several functional domains for controlling the properties and the encapsulation of overall functional units in the dendrimer allows for the isolation of the active site. Overall structure has a great deal of similarity with a network of active sites as located in any other compatible biomaterial because of the presence of dendritic scaffolds which operate in a highly selective manner to distinctly define the internal and external functions. The sections in the text ahead describe the various categories of dendrimers with a targeted approach to make dendritic giant molecules which are very active from biological as well as chemical point of view and are thus very useful for different biomedical, biochemical and biophysical applications.

The branching units of dendrimers can be a number of biological variants such as those of peptide antigens, saccharides, amines, polyesters, melamine, dialkyl malonate esters and many others which impart the desired biological and biochemical properties to the dendrimer structure as a whole. To engineer the dendrimer structure for biomedical and drug delivery applications, PAMAM or PPI dendrimers **[9, 33]** can be synthesized by functionalizing the outer periphery of the dendrimer surface with suitable and complementary biological molecules. This method can also be used to design the dendrimers that possess biologically active molecules as structural building blocks.

Polyamidoamine dendrimers

In 1985, Tomalia synthesized branched Polyamidoamine (PAMAM) dendrimers by the divergent method which also known as ‘starburst dendrimers’. These dendrimers are one of the very breakthrough molecules in the dendrimer field and are extremely useful with respect to their properties and engineering potential. During the synthesis of a typical PAMAM dendrimer molecule, ethylene diamine as the core undergoes a Michael addition reaction with four equivalents of methyl methacrylate as branching units (**Scheme 1**) **[11]**.



Scheme 1. Synthesis of PAMAM dendrimers.

In this step, a characteristic aim accomplished is the doubling of terminal groups. The subsequent four equivalents of ethylene diamine are coupled through peptide bond formation, which results in the establishment of the primary amine functionality to the surface of a practically, 0.0 generation PAMAM dendrimer molecule. These two simulations are repeated for each subsequent generation

Finally, ester terminated dendrimers of this type can be converted to a carboxylic acid morphology so as to form a

half generation dendrimer, i.e. a generation of 0.5 PAMAM. Interestingly, both amino terminated as well as carboxylic acid–terminated dendrimers are commercially available. Products up to 10 generations have been prepared with a molecular weight more than 930,000 g/mol. The Sigma Aldrich commercialized PAMAM dendrimers as Trade name Starburst TM. Selected physicochemical properties of generation (0-10) PAMAM dendrimer are listed in **Table 1 [44, 45]**.

Table 1. Physicochemical properties of generation (0-10) PAMAM dendrimers.

Generation number	Molecular Weight	Diameter	Number of NH_2 at surface
0	517	1.4	4
1	1430	1.9	8
2	3256	2.6	16
3	6909	3.6	32
4	14215	4.4	64
5	28826	5.7	128
6	58048	7.2	256
7	116493	8.8	512
8	233383	9.8	1024
9	467162	11.4	2048
10	930000	12.9	4096

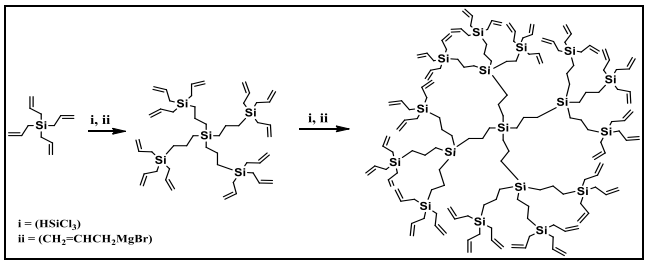
Glycodendrimers

These are the dendrimers which possess a carbohydrate unit in their structure and can be categorized into three distinct types, *viz*. carbohydrate-branched dendrimers, carbohydrates as a core in dendrimers or carbohydrate-based dendrimers **[46-48]**. Glycodendrimers have carbohydrate frameworks that attract both carbohydrate chemists and biologists due to their ability to identify lectins and increase carbohydrate–protein interactions. These features of glycodendrimers make them useful molecular materials in the field of glyco and biomedical sciences. Investigations of the carbohydrate coated dendrimer molecules have largely focused on the two dominant classes of dendrimers, namely the PAMAM and PPI dendrimers. Both dendrimers have been tagged with glycosyl derivatives through urea, thio-urea and amide bonds **[49, 50]**.

The supramolecule cyclodextrin can also be a highly useful agent for synthesis of dendrimers which facilitate for the synthesis of carbohydrate-centered dendrimers by favouring the combination of multivalent structures with an ability to form complexes with small hydrophobic molecules within the cavities persisting along with cyclodextrin moiety **[51]**. Molecules of this nature can be designed specifically for use in targeted drug delivery applications. Numerous examples prevail, that highlight the synthesis of carbohydrate based dendrimers synthesized via inherent glycosidic linkages **[52-54]**. Glycodendrimers have been used for a number of biologically relevant applications. Most notably, these have been optimally employed to study the protein-protein interactions that are involved in several intracellular recognition events. In comparison to other frameworks which have been engaged to study such interactions, dendrimers hold much more significance and reputation due to their useful structural attributes of size and low polydispersity. The eye catching aspect is that the size of a glycodendrimers can be varied in a gradual manner depending on the specific generation of the dendrimer being used.

Silicon based dendrimers

In 1989, the first synthesis of silicon based dendrimers initiated by H. Uchida and co-workers were successfully accomplished **[55]**. After 1990, several methodologies have been developed by Vander Made, Van Leeuwen, Roovers and Syferth for synthesis of carbosilane dendrimers and describe their use in biological applications **[56-59]**. In 1992, Vander Made et al have reported the synthesis of carbosilane dendrimers by using tetraallylsilane as core with allyl magnesium bromide (CH_2=$CHCH_2MgBr$) as branching units in the presence of O-alkenylation reagent hydrosilylation ($HSiCl_3$) (**Scheme 2**). Currently, several research groups developed applications of carbosilane as new versatile, lectin sensors and also as a novel drug carrier for active targeting drug delivery system. Besides, the use of carbosilaneglyco dendrimers as a bioactive molecule against Shiga toxins, dengue viruses, relapsing fever borrelia, and hemagglutinin and neuraminidase of influenza viruses have also been established **[60-62]**. The numerous research groups also define characteristic functionalization of carbosilane dendrimers with carbohydrate ligands at terminal positions which are required for chemical ligation. This is involved by a description of all types of coupling reactions between carbohydrate and carbosilane dendrimer functionalities used for the synthesis of carbosilaneglyco dendrimers.

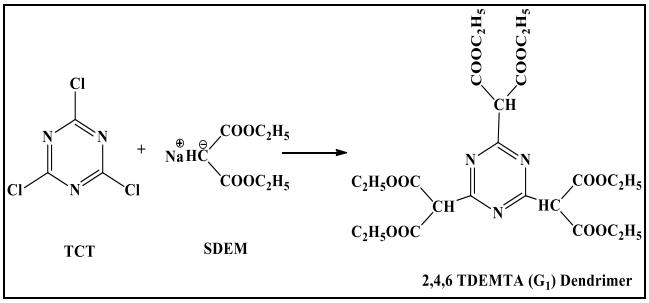


Scheme 2. Synthesis of carbosilane dendrimers by van der Made's approach.

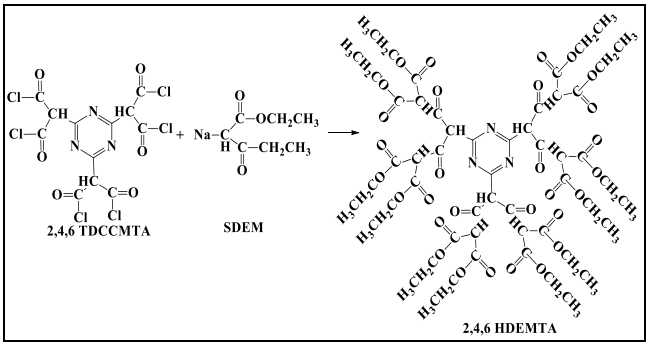
Peptide dendrimers

Peptide dendrimers can be understood as highly branched structures of synthetic origin which constitute peptide bonds. Just like those of glycodendrimers, peptide dendrimers are also categorized into three distinct classes. First of class of peptides and made up of tri functional amino acids that can be used as branching points, while the second class only marginally differs from these in having their periphery functionalized with peptide chains **[61, 62]**. Lastly, third class of peptide dendrimers is grafted peptide dendrimers, which consist of either biomolecules amino acids or organic molecules as the branching core components and peptides or proteins as surface functionalized molecules. As a consequence of the dendritic architecture, peptide dendrimers hold some unique and dynamic potential in a number of related allied fields such as those of biomedical and biochemical. This can be very well judged from their use in the form of synthetic

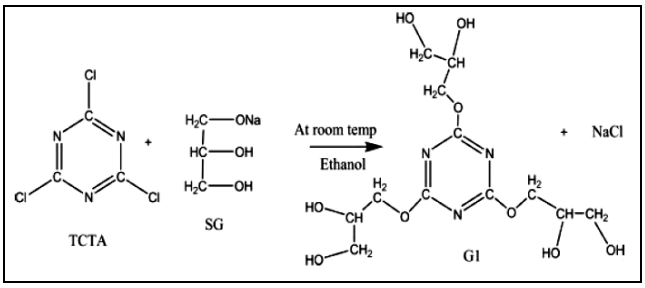
vaccines, adjuvants, protein-like structures, mimicking or redesigning of ion-channelized structures, in the study of inter-cellular interactions and the potential for being usable as drug carriers. These dendrimers vary in molecular weight variants with species of 2 kDa as well as lasting extents of maximum value of 100 kDa, including their domain. Their synthesis can be controlled through synthetic methodology and the products of consistent size, architecture and composition. The text ahead sheds some light on three main categories of peptide dendrimers and their potential applications in the various fields.



Scheme 3. Synthesis of TDEMTA G1 dendrimers.



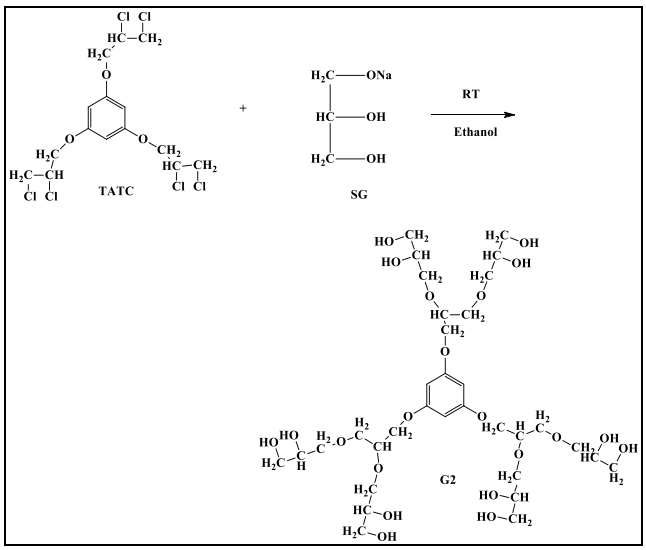
Scheme 4. Synthesis of HDEMTA G2 dendrimers.



Scheme 5. Synthesis of TGTA G1 dendrimers.

Melamine and triazine based dendrimers

Synthesis of melamine based 2,4,6-tridiethylmalonate-triazine (TDEMTA) (**Scheme 3**) and second tier (G2) 2,4,6-hexadiethylmalonate-triazine (2,4,6-triethylmalonate-triazine (2,4,6-HDEMTA) dendrimers (**Scheme 4**), with excellent physicochemical properties have been reported by Singh et al. **[63]**. Studies on the spectroscopic and thermal decomposition have notified and selectively pointed out the similarities in the structures of first and second tier dendrimers. However, a basic difference that has been pointed out is of the degree of polymerization. In case of G1 dendrimers, the molecular weight is 3826.14 g/mol, while for G2, it is 2476.85 g/mol, with degrees of polymerization being six and two, respectively. This clearly highlights those more branching results in inhibition of the intra- and homomolecular linkage for molecular associations leading to linear linkages due to more stability.



Scheme 6. Synthesis of tri (1,3,5-triglycerate) trazine G2 dendrimers.

The triazine-derivative G1 1,3,5-triglyceratetriazine (TGTA) (**Scheme 5**) and G2 tri(1,3,5-triglycerate) (**Scheme 6**) based trazine dendrimers with glycerol as a branching unit having unique physicochemical properties were also reported by Singh et al. **[64]**. In this way, dendrimers can be water soluble when its terminal group is hydrophilic such as the -OH group. It is also possible to design or synthesize a water soluble dendrimers with internal hydrophobicity, which will facilitate the passage of hydrophobic materials through the dendrimer interior.

A dendrimer molecule can also be synthesized by means of a redox reaction between the nanoparticle core (redox active nanoparticles) and the dendritic wedges. Despite their isolation, some of the redox molecules remain uncoupled and thus still hold the capacity to react.

Dendrimers are also efficient delivery vehicles for sending the medicated formulations to the affected location inside a patient's body. The presence of diols at the terminal chains of a dendrimer molecule assists in the encapsulation of gold nanoparticles onto its structure. Systems like these have been found to be highly useful in photo thermal therapy and imaging.

Biodegradable dendrimers

Through the proper selection of the monomer(s), biodegradable dendrimers can also be synthesized, that degrade due to the presence of biocompatible building block presence in their structure through in vivo means. 14 Suitable monomers for biodendrimers synthesis include α-hydroxy acids, sugars, amino acids, fatty acids, poly(ethylene glycol) (PEG), poly(caproic acid) (PCL) and poly(trimethylene carbonate) **[65]**. A number of factors that affect the degradation rate such as those of the strength of chemical bonding between the monomers, hydrophobicity,

generations and molecular weights of the dendrimers and also the chemical reactivity of the overall macromolecules.

Seebach and co-workers reported the first ever enzymatically biodegradable dendrimer in 1996 **[66]**. They examined the polyester based dendrimers on the basis of the initial core assembly. These polyester dendrimers got easily degraded by the bacterial enzyme poly (3-hydroxybutyrate)-depolymerase into hydroxybutanoic acid and a trimester of 1,3,5-benzenetricarboxylic acid with hydroxybutanoic acid. After gaining an insight into these known biodegradable dendrimers and the corresponding degrading enzymes involved, Grinstaff, Zoka and co-workers developed several polyether-ester based dendrimers and have used one of these, composed of succinic acid and glycerol for the encapsulation of anticancer drug 10-hydroxycamptothecin **[67,68]**. Spectral analysis through 1H NOSEY indicated the efficient encapsulation of the drug in the dendrimer core. The encapsulated drug was also tested for its efficacy against the breast cancer cell line, which showed that it possessed a higher cytotoxicity.

Synthesis of dendrimers

Generally, two main synthesis routes for dendrimers have emerged, namely the divergent and convergent approach.

Divergent synthesis

In general, highly symmetric dendrimers are synthesized through divergent approach. However, recently, the scientists have taken up the possibility of synthesis of differently functionalized dendrimers through which they have put forward a number of differently functionalized dendrimers with variable functionality present on their surface **[69,70]**. Moving ahead, Denkewalter and co-workers were granted patent on the first divergent synthesis of dendritic polypeptides having the amino acids as their constituent monomeric building block **[71]**.

The divergent route of dendrimers synthesis was also reported by Vögtle, Meijer Mülhaupt, Tomalia and Newkome **[9, 72]**. The divergent route for dendrimer synthesis involves the beginning of the growth at a multifunctional core. This is followed by the gradual stepwise addition of binding units, which leads to the establishment of larger dendritic structures with a consistently increasing number of chains and reactive functional groups present at the surface (**Fig. 2**). On the other hand, in the divergently approach, put forward by Newkome and Tomalia, the growth of a dendrimers originates from the core molecule. Each branching cycle leads to the addition of one more number of branches at particular sites of the dendrimers molecule, conventionally known as a generation to the existing dendrimer framework. Thus, the generation number of a dendrimer molecule is equal to the number of reaction cycles performed during the synthesis of a dendrimer. This can be easily computed by considering the number of branch points as one attached from the core to the surface of the overall molecule **[73-75]**.

The poly (propylene imine) dendrimers are very popularly employed for research based applications and have been developed through the use of a 1,4-diaminobutane core functionalized with tertiary amines serving as branch points **[76]**. The reaction scheme for the synthesis of PPI dendrimers is basically a repetition of the Michael's addition reaction between acrylonitrile and primary amines. The heterogeneous catalysed hydrogenation of the nitriles, facilitate a number of primary amines at the surface of the dendrimers. Both the reaction steps involved in their reaction can be carried out to bring about extremely high conversion efficiency with higher selectivity as well.

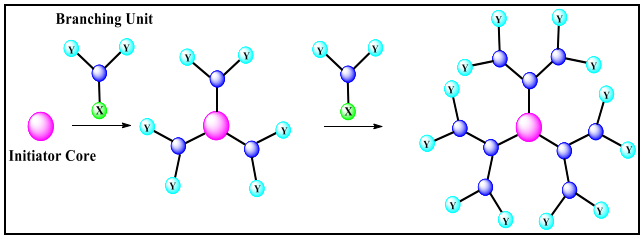


Fig. 2. Divergent synthesis of dendrimers.

Convergent synthesis

On the contrary, in the convergent approach, as proposed by Hawker and Frechet, the synthesis proceeds from the dendron molecular surface (periphery) to an inward direction towards the central core (focal point) and are directed through the core region of the dendrimer (**Fig. 3**) **[77-82]**.

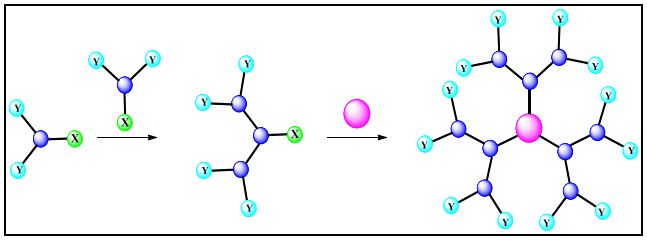
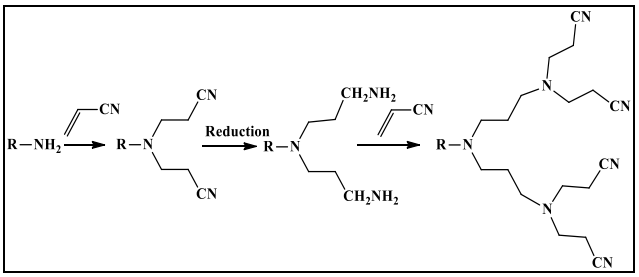


Fig. 3. Convergent synthesis of dendrimers.

The intermediate products obtained through the convergent synthesis of dendrimers are easier to purify and are generally assumed to be more homogeneous than their counterparts produced by divergent synthesis. The strategy for convergent synthesis is often restricted to the dendrimers with low generation and starts from the surface and ends up in the core, when the dendrimer segments (dendrons) are coupled together. In this manner, only a limited number of reactive sites get functionalized in each step which ensures a smaller number of possible side-reactions per step. This implies that each synthesized generation of the dendrimers can be purified, although purification of high-generation dendritic tissues is too difficult because of the increasing structural similarity in between the reactants and the formed products **[83, 84]**. However, with proper purification after each successive step, convergent approach gives the dendrimers without any defect. The convergent approach is also the preferred one because it does not allow the formation of higher generations. Due to the presence of steric problems, which

occur in the reaction of dendrons and the core molecules. The current approach that is most popular for dendrimer synthesis was put forward by the efforts of Frechet, Miller and Moorie **[85-89]**.

Dendrimers are synthesized in a repetitive sequence of reaction steps, in which each repetitive monomer unit leads to a higher generation (G) dendrimers with an increase in molecular weight. The branching of monomer unit takes place in a stepwise manner and thus it is possible to precisely control the overall size, shape, dimension, density, polarity, flexibility and the solubility of the molecule by optimum choice of the different building or branching units and the surface functional groups **[9, 10, 90-106]**. Moreover, these types of dendrimers can use organic molecules as their constitutional entities and thus possess significant physical and chemical properties of interest. In a generalized sense, dendrimers are regular, highly branched structures and specific dimensions which formed multivalence as like those of the small proteins. During 1978, Fritz Vogtle and co-workers were the first to introduce the synthetic dendrimer chemistry **[107]**. They reported the first ever synthesis of cascade molecules using an iterative scheme of reaction steps to achieve the synthesis of a higher generation (**Scheme 7**).



Scheme 7. First synthesis of a cascade molecule.

The reaction of the monoamine as a starting material using acrylonitrile via Michael's addition was reported for the synthesis of dinitrile and it was subsequently reduced to terminal diamine which acts as a branching unit. The molecule was used with the same reaction sequence for the synthesis of heptamine.

In 1984, the first family of hyperbranched series of macromolecules, also termed as "starburst dendrimers" was put forward by Tomalia and research group. Many other investigators have also developed synthetic methodologies to make these dendrimers and have also proposed their applications. During the early years of 1980's, a synthetic methodology as well as some specific applications of dendrimers was forwarded by Newkome **[12]**.

Characterization of dendrimers

Dendrimers are hyper branched and globular macromolecules having a specific architecture with two distinct parts; (i) center most molecule is a core having a single atom or group with two or three equal chemical functionality, (ii) branching units having repeating units with at least one branch junction is responsible for growth in bi-furcational and organized in a geometrical manner and which is play a key role in the properties of dendrimers. Synthesis and development of applications in various fields, there is a critical need of analytical techniques for characterization of dendrimers.

Nuclear magnetic resonance (NMR) spectroscopy

NMR is the most widely and reliably employed methods being considered for the characterization of the dendrimers. The analysis through NMR really argues very well for the dendrimers since they enable the provision to analyse their synthesis in a stepwise manner. Secondly, these techniques also enable better and more proper understanding of the formation of high generation dendrimer by giving information about the chemical transformations the chemical groups undergo. The 1H and 13C NMR techniques are right now most widely employed for the structural characterization of organic dendrimers like those of PPI, polyphenylester and poly (ether ketone) dendrimers **[108]**. For a higher generation or complex structures or complex pulse sequences need to be very efficiently as well as effectively analyzed. This is done with two dimensional H, HCOSY for polyphenylacetylene **[109,110]** or polyaryl **[111]** dendrimers. Likewise, 1H and H-NOESY NMR variations are used for studying and analyzing PPI dendrimers **[112]** and H, H-TOCSY methods are employed for melamine dendrimers **[113]**. The diversity of integrated NMR techniques is so deep that even the three dimensional NMR techniques such as those of 3D HMQC-TOCSY and 3D NOESY-HSQC have been employed for the characterization of PPI dendrimers **[114]**. For dendrimers with heteroatomic composition, besides 1H and 13C NMR, the resonance of the heteroatom provides very valuable information; this is highly applicable and well-established fact for phosphorous based dendrimers. The sensitivity or accuracy can be very well judged from the performing behaviour of 31P NMR, in which the environment around the sample is so sensitive to the small changes in the vicinity so that it allows one to differentiate in between the layers up to the fourth generation and at least the three most external layers for higher generations, up to G12 **[115]**. Some very complex structures which possess coupling between some phosphorous atoms can be entirely characterized using 31P NMR technique **[116]** even when there is a coexistence of two types of branches in the same dendrimer molecule. Similarly, silicon-containing dendrimers are generally characterized using 29Si NMR, **[117]** despite a very low amount of 29Si being present in silicon derivatives. Multidimensional NMR methods using silicon such as 29Si and 1H, 13C, 29Si; 3D-NMR **[118]** variations have also been applied to the silicon-containing dendrimers. 15N NMR has been very rarely used, but it is highly helpful in the characterization of PPI dendrimers in order to detect their selective protonation mechanism, first on the surface of the second generation, then at the core and then at the level of the first generation **[119]**.

Fourier transform infrared (FTIR) spectroscopy

FTIR spectroscopy is mainly employed for the routine and timely analysis of chemical transformation being facilitated at the surface of dendrimers, such as the elimination of nitrile groups during the synthesis of PPI dendrimers, **[120]**

the generation of hydrogen bonding in PPI glycine functionalized dendrimers or the intended elimination of aldehydes during the synthesis of PMMH dendrimers **[121]**. Further, in-detail IR-analysis with quantitative deductions was also carried for phosphorous dendrimers **[122]**. Similarly, near IR-spectroscopy has also been used to characterize the delocalized the k-k stacking interactions between the end groups of modified PAMAM dendrimers **[123]**.

Ultraviolet visible (UV-vis) spectroscopy

UV-vis spectroscopy can be employed to monitor the synthesis of dendrimers, as shown for the characteristic organ-platinum dendrimers in which the growth and decay of metals to the ligand charge transfer band is observed **[124]**. It is a characteristic instrumentation in the sense that the intensity of absorption band obtained through it is necessarily proportional to the number of chromophoric units present embedded within the molecule being analyzed and this forms the basis for the use of this technique to test the purity of PPI dendrimers having azobenzene as end groups, **[125]** for phosphorous dendrimers having azobenzenes incorporated within the branches, **[126]** or double-layered carbosilane dendrimers **[127]**.

However, surprisingly, a deviation from the Beer-Lambert law is observed for G4 and G5 PPI dendrimers, which possess methyl orange as the terminal groups **[128]**. The technique of UV-visible spectroscopy has also been used to understand and elucidate the morphological information. The dendrimers from G0 to G6 functionality exhibit an intense change in the absorption maximum from those of G3 to G4, consistent with a transition from an open to a more globular shape **[129]**.

Mass spectrometry

Due to their characteristic dependence on the mass being a limitation too (in some cases), classical mass spectrometry techniques such as those of chemical ionization or fast atom bombardment can be used merely for the characterization of small dendrimers (3000 D). For high molecular weights, techniques developed for the study and analysis of proteins and polymer behaviours need to be applied. For instance, Electro-Spray Ionization can be used for the analysis and investigation of dendrimers with reference to their optimization to form multi charged species. This technique has also been applied to PPI dendrimers **[130]** as well as in PAMAM dendrimers up to tenth level of generation moving from the core towards the outside **[131]**. The Matrix Assisted Laser Desorption Ionization Time of Flight (MALDI-TOF) Spectroscopy was used for the analysis of unlimited masses. This has also been employed for the characterization and evaluation of the purity of aromatic polyesters, polybenzylacetylenes, **[132]** PAMAM, **[133]** silicon dendrimers **[134]** and phosphorous dendrimers **[135]**. The imperfections that are generally encountered in almost all the cases of high generation are routinely attributed to chemical defects. However, the fundamental operation of this technique does question absorbance at the wavelength of laser used for desorption by the dendrimers. Moreover, this technique is also highly sensitive to the operational experimental conditions, especially for the type of matrix being used **[136]** and the presence of ions, as shown by post-source decay investigations. Similarly, secondary Ion Mass Spectrometry was applied to a series of bis (methoxy) propionic acid-based dendrimers **[137]**.

Physicochemical characterization

Dilute solution kinematic parameters such as those of rheology and in particular, the viscometric studies; can be used as analytical probe agencies to investigate the morphological structural features of dendrimers. Dendrimers should exhibit a maximal dependence behavior on the intrinsic viscosity [η] upon their generation. This is so because till a saturated generation level is reached, the volume grows faster than the molecular weight beyond which the behavior is exactly the contrary. This behavior is experimentally observed in a number of dendrimers with definite series. The maximum of intrinsic viscosity occurs at different generations for different dendrimers, characteristically depending on the density of the constituent dendritic branches **[138]**. For instance, G3 phosphorous dendrimers with two types of end groups **[139]**. G4 dendrimers have been optimized for PAMAM functionality, **[140]** G5 for PPI **[141]** with two types of end groups.

Application of dendrimers

Currently, the several exciting developments and methodologies for the synthesis and characterization of dendritic materials are being driven through their distinct and multifold uses which include their incorporation in the form of structural materials, drug loading matrices, microelectronic circuiting, coatings, biomedical materials and building blocks for nanotechnology based networks **[93,142]**. Till date the expansions of multidisciplinary application of dendrimers have been immensely increasing and encouraging with their incorporation into the development of supramolecular chemistry, electrochemistry, photochemistry, nanoparticle manufacturing, pollution management, dye decolourization, epoxy resins curing, catalysis, drug delivery and gene transfection. In the recent years the use of dendrimers in the drug delivery systems has received some special attention with a sharp interest paid to their utilization and involvement in the biomedical sector.

This work sheds some light on the synthesis of dendrimers, systematic analysis, understanding of dendrimers structure and its components, understanding of mechanisms of drug delivery, the effect of different physical and chemical factors on the dendrimers properties and characterization; the recent work has been reported as the applications of dendrimers. In the domain of biomedical and cutting edge diagnostic technology, dendrimers have major applications in the area of gene and antisense therapy, magnetic resonance imaging and in boron neutron capture therapy **[6-7].** The special attributes of dendrimers which include advancement in terms of their functional nature, making them biodegradable and optimizing their release based features, can be very good assets for the development of specific and improvised drug delivery

systems. The engineering of dendrimers has been so fine-tuned that it has enabled them to be used as cancer drug carriers with controlled degradation.

Drug delivery

The discovery and final formulation of new drugs is a long as well as costly process. In general, a new drug takes almost 12 to 15 years to be developed and ready in order to bring them in commercial scale amongst the consumer section, at an average expenditure of above $800 million **[143, 144]**. In this context, the real benefit of the structural attributes of dendrimers can be realized by the designing of effective drug delivery systems that could be used for the drugs developed in the past, but failed to be brought into the market due to some control of their release and delivery potential. With the use of dendrimers, the novel drug delivery systems could be formulated capable of enhancing the effectiveness of the overall drug delivery by ensuring its sustained release in gradual time and at a specific target **[145]**. Through the control of time and effective location of a typical drug delivery system, side effects of the corresponding drug can be minimized while drug activity can be maximized. This would also enable the intake of a much lower amount of drug in a number of cases as compared to a number of other drugs suffering from this problem. This feature also enables much better and easier patient compliance. Some strategies that are employed to achieve a controlled release of the drug include chemical or enzymatic reaction, diffusion through a matrix or solvent activation.

At present, two common strategies which are mostly practiced are tagging of drug with liposomes and the use of polymeric systems. However, both of these strategies have some problems with their formulation with liposomal based drug formulations suffering from poor stability under physiological conditions and linear polymers being polydisperse in nature. Regarding these technical bottlenecks, dendrimers have just served as a blessing as these are comparatively safer, possess better selectivity and thus have better potential for being used as drug delivery candidates. These are highly selective in nature from the point of view of specific targeting of the desired tissue, which is the backbone of an efficient drug delivery system and give a much better and promising future to be used as treatment models for several disorders. Other useful attributes of dendrimers are characterized by their very small size, polyvalent nature, monodispersive action, stability, which impart the dendrimers systems their precision and selectivity.

In particular, the cancer treatment has received a much needed boost from these systems with dendrimers being used for delivery of anticancer drugs (methotrexate). Similarly, a significant attribute has been achieved in the prevention of HIV. In a similar manner, ocular bioavailability of the drug pilocarpine has been enhanced through the use of dendrimers. The use of dendrimers for drug delivery system development is based on the delivery of a nanoparticle loaded with drug to specific affected locations of the body. The advantage of the system seems to be eminent from the fact that it enables the drug to be loaded at the terminal, surface as well as its encapsulation within the corresponding branches of a dendrimers. Thus, in a nut shell with so many controllable features, dendrimers enable increased bioavailability, sustained, controlled as well as the targeted release of the drug, which have been just the key ingredients of an ideal drug delivery carrier. With this much control being exercised at the right amount of drug being delivered at the right location within the body, there's a significant reduction in the amount of drug being delivered in the body, thereby also lowering the risk of toxicity being developed while the corresponding therapeutic efficacy of the drug increases. These features of dendrimers make them reliable, safer, selective and comparatively more precise systems of drug delivery.

The chemical and structural attributes of dendrimers which make them to be used as excellent drug delivery carriers include their low polydispersity index, multiple functionality achieving sites and a well-defined, easily controllable and the requirement based adjustable nature which is all the features or traits of chemical attributes of the system **[146]**. Some other salient features of dendrimers are their enhanced permeability and retention effects that also allow them to target only the tumour cells in preference over the normal cells **[147]**.

Two common methods by which dendrimer molecules are engineered for drug delivery are either the encapsulation of the drug with dendrimers or the design of dendrimer-drug conjugates. Encapsulation of the drug makes use of either the steric bulk of the outer periphery of a dendrimer molecule or specific interactions between the dendrimers and the drug are optimized to trap the drug inside the dendrimer. On the other hand, dendrimer drug conjugates carry the drug attached to the external periphery of drug only. Most of these designed conjugates are prodrugs, which are inactive or have decreased activity in comparison to the free parent drug. Rapid progress has been witnessed in the development of dendrimer carriers that can be monitored using UV spectroscopy and optimized for the delivery of anti-cancer drugs. Both encapsulation and conjugation strategies have their own mutual benefits in the dendrimer mediated drug delivery.

Encapsulation of drugs in the dendrimers favors their sustained release while dendrimer drug conjugates enable efficient, targeted release of the medicated formulation. The application of dendrimers being used as carriers of drug delivery is receiving some auspicious attention with recent reports of the development of cascade release of dendrimers and additional ways to release drugs. Some studies on the use of dendrimers as in vivo drug delivery carriers have been reported. In one such case, cisplatin has been complexed with carboxylate surface groups of PAMAM dendrimers which could lead to enhance its solubility to an extent of ten present with respect to the free drug **[148]**. These conjugates were further shown to target subcutaneous tumours in the mice with an enhanced permeation and retention effect **[149, 150]**. On the same lines, a fatty acid functionalized dendrimer was shown to bind another anti-tumour drug, 5-fluoracil which further showed almost double oral bioavailability in rats as compared to freely administered 5-fluoracil **[151]**. The methotrexate conjugated with PAMAM dendrimers and used as antitumor targeted carriers **[152]**.

In case of dendrimer molecule coupled with methotrexate, the dendrimer molecule has been modified using folate as a targeting agent with an aim to inject flurophore and methotrexate in the injured mice. The dendrimer mediated delivery was found to be so effective that its concentration in the mice suffering from cancer was found to be five to ten times higher than that of drug formulation without the use of folate ligand. To add to this is the significant effect this dosage in for reducing the rate of tumour affected cells. A number of other manipulations of dendrimers have been devised which can be used as antiviral infection curers by means of improved drug delivery mechanism and routes **[153-155]**. Not only the drug delivery, but also, the procedure of gene delivery has seen some serious and major improvements with a variety of positively charged dendrimers being used to form complexes with DNA and further transfect the cultured cells with lower toxicities and far better efficiencies as compared to conventionally employed therapeutic agents **[156-162]**. The attributes of dendrimers which can serve as boosts for their use in drug delivery applications include their biodegradable nature and optimize release of the formulation from the system as a whole.

Tissue engineering

In a significant trial, Grinstaffet al has shown that dendrimers possess high functional densities and low solution viscosities which make them very useful to be used in wound healing applications in the form of injectable sealants especially for handling corneal wounds **[163-165]**. In this work, the peripheral boundaries of biodegradable polyester dendrimers have been functionalized with surface active groups that are capable of cross linking and forming insoluble hydrogel based matrix like systems upon getting activated, e.g. in case of polymerization by using ultraviolet light. By following this procedure, the scientists have successfully sealed the corneal lacerations. Efforts are actively being made on the optimization of the use of such materials for many other medically tough ophthalmological surgeries.

Magnetic resonance imaging

One of the earliest discovered applications of dendrimers was their use in the form of carriers to fasten and improve the overall efficacy of Magnetic Resonance Imaging (MRI) contrast agents **[166, 167]**. Literature is already replete with a number of review articles that highlight the applications of dendrimers in the domain of diagnostics **[168, 169]**. Modification of PAMAM dendrimers with the chelating ligand diethylenetriaminepentaacetic acid through the introduction of a thiourea linkage, were to image the MRI scans of blood vessels. These engineered dendrimers also increased the blood circulation times upon their intravenous injections as conjugates of gadolinium. PPI dendrimers have also been reported to be synthesized with the help of Gd (III) -DTPA ligands **[170]**.

In a related attempt with this research, the Gadomer has been employed and incorporated in dendrimers based on the core morphology of 1,3,5-benzoic acid, also possessing lysine units as branching units with Gd-DTPA molecules also identified along with the Gadomer **[17]** has been especially suited and employed for these kinds of dendrimers due to their specially suitable and biocompatible nature such as those of good elimination rate, globular nature for being a dendrimers derivative. In addition, dendrimers using this moiety have also been developed for MRI usable for both targeting and imaging of components **[171]**.

Vaccines

Dendrimers with peptide backbone have been actively employed for the development of improved vaccination and immunization. One such configuration of dendrimers is a multiple antigenic peptide (MAP) dendrimer system, put forward by Tam et al. **[172, 173]**. In their work, Moreno *et al*. have put forward an interesting illustration in which by a using Plasmodium falciparum T and B cell stimulatory peptides, the MAPs dendrimers has been modified for developing vaccine applications **[174, 175]**. In a similar manner, Ota et al has shown that MAPs could be processed in antigen containing cells in the same way and resulting in a stronger immune response emanating through the action of cytotoxic T-cells **[176]**.

Electronic devices

Organic electronic devices such as organic integrated circuits, organic FETs, organic thin-film transistors, organic solar cells, organic field quenching devices, organic light-emitting transistors, light-emitting electrochemical cells, organic optical detectors, organic photoreceptors, organic laser diodes, and organic electroluminescent devices are described as linear or branched dendrimer compounds incorporating a specify component and serve as hole-injecting, hole-transporting, electron transporting, or hole-blocking materials **[177, 178]**. The researcher has fixed flurophores on the periphery of different generations of dendrimers, which can absorb two photons **[179]** and can be used as fluorescent markers for biomedical applications such as Nano dots.

Catalysis

In the field of catalysis the dendritic molecule has emerged as potential materials with various dendrimers based catalysts being applied to catalytic reactions **[180-193]**. The dendrimers having controllable nanoscale sizes, symmetrical, chemically reactive surface and favourable configuration properties make them useful not only in catalytic application, but also in non-catalytic ones such as nanoscale reactor systems. There are various examples of dendrimers catalyst in organometallics **[194-196]** such as ferricenic sandwich with better redox catalytic properties.

In last two decades, many works have been done on the catalytic behaviour by pioneering research teams in the periphery, the scaffolding, or on the core of dendrimers. The main aim of the entire researcher is to find ideal catalyst with high catalytic efficiency, selective for whatever reaction, versatile (substrate, metal, conditions), easily recoverable or recyclable and longevity (durable and stable). For an instance, PAMAM dendrons based on silica-coated magnetic nanoparticles has used for hydro

formylation reaction with the very high catalytic efficiency **[197]**.

Biosensors

A compilation of dendrimers, constituted either by distinct monomers or the nature of linkage **[198, 199]**. The rapid progress of the nanotechnological and advanced nanomaterials production offers significant opportunities for several applications such as detection and bioremediation in broad range of environmental pollutants. Due to integration of analysis techniques and nanotechnology, it has become possible to develop miniaturized, rapid ultrasensitive and inexpensive methods for *in-situ* and environmental monitoring devices. Specific examples of nanomaterials-based and biological sensors with applications in environmental monitoring have already been reported **[200-205]**. A polyamidoamine dendrimer with peripheral 1, 8-naphthalimide groups capable for acting as a PET fluorescent sensor for rare earth and metal cations has been reported. The presence of metal ions was found to evoke a photo induced electron transfer leading to an enhancement in the fluorescence **[206, 207]**.

Conclusion

In conclusion, dendrimers have received increased attentions among the researchers due to its unique structure, properties and applications. For the formation of the dendrimer, covalent bond formation is more important which is followed by metal-ligand coordination bond formation and non-covalent bond formation. A range of applications have been reported particular in the area of chemistry and biology for example in the field of drug deliver, catalysis, sensing, etc.

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