Dendrimers: Synthesis to applications: A review

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ABSTRACT

Dendrimers are new class of polymers, first invented in 1978 by Vogtle. Unlike linear polymers, dendrimers have special properties such as nanometer size range, narrow polydispersity, high degree of branching and presence of internal cavities which allows them to be used in many applications. Dendrimers can be mainly synthesized by either divergent or convergent routes. Recent advances lead to different routes for dendrimer synthesis which gives control over molecular architecture and allows incorporation of different functionalities in dendritic architecture. As a result new types of dendrimers with different functionalities have been synthesized. Unique properties of dendrimers have attracted attention of several researchers from interdisciplinary fields. This led to applications of dendrimers in various applications for e.g. various routes of drug delivery, gene therapy, cancer therapy, catalysis and in membrane technology. This review covers approaches for dendrimer synthesis, and their potential applications such as drug delivery, gene delivery, cancer therapy, catalysis and in membrane technology.   © 2014 Trade Science Inc. - INDIA

INTRODUCTION

Traditionally polymer science has mainly focused on linear polymers. Since 1970s a great deal of interest was increased in highly branched macromolecules because of their unique properties which facilitate their use in "Host-Guest Chemistry"[1]. One such branched macromolecule which was discovered by Vogtle et al.[2] in 1978 termed as "Dendrimer". Then in early 1980s, Denkewalter et al. reported three patents[3-5] on polylysine dendrimer, Tomalia et al.[6] published his work on "Starburst dendrimer" and Newkome et al.[7] synthesized "Cascade molecules" laid the foundation for dendrimer synthesis. Dendrimers are large and com-plex molecules having very well-defined chemical structures.

They possess three distinguishing architectural components, mainly[6]

(a) An initiator core,

(b) An interior layer (generations), composed of repeating units, radially attached to the initiator core and

(c) Exterior (terminal functionality) attached to the outermost interior generation as shown in Figure 1.

Dendrimers are synthesized mainly by either "Divergent" or "Convergent" route. With the time and research in the field of dendrimer synthesis, new approaches have also been evolved. Dendrimers offer

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plenty of advantages compared to other architectural forms of polymers. For example, dendrimers having nanometer size range, narrow polydispersity, high degree of branching and presence of internal cavities. Therefore, dendrimers can easily be used as polymeric materials in fields such as catalysis[8], for drug-delivery systems[9-11], particularly useful of applications for cancer therapy[12,13], gene delivery[14] and as membranes[15]. Present review covers different approaches for dendrimer synthesis and their potential applications.
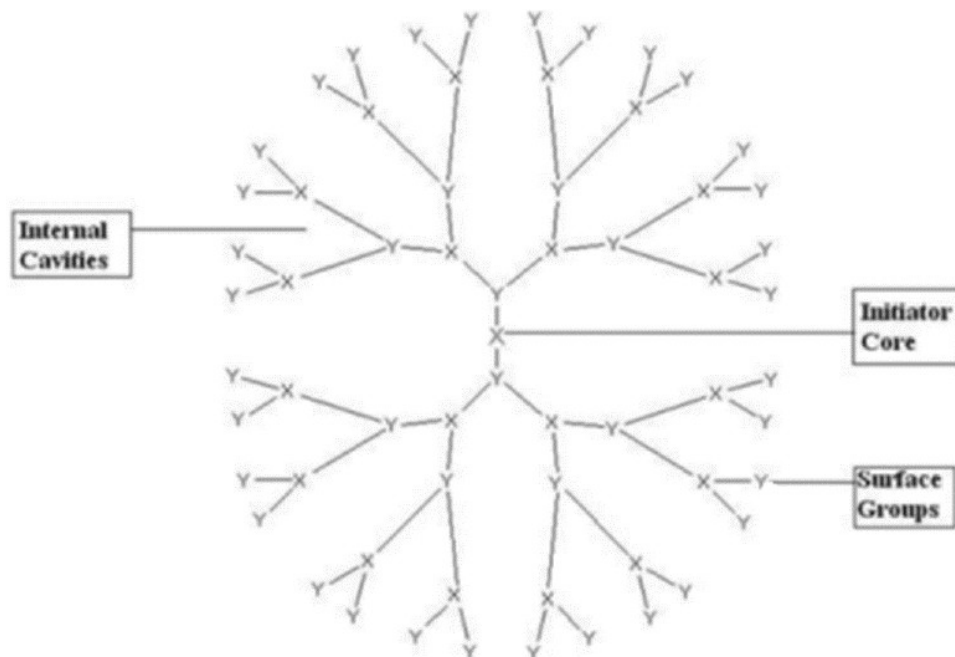

Figure 1 : Show dendrimer with structural components initiator core, surface groups and generations

ROUTES OF DENDRIMER SYNTHESIS

Since the first ever reported dendrimer in Vogtle et al. (1978), mainly two methods have evolved in dendrimer synthesis. Most syntheses of dendrimers involve the repetitious alternation of a growth reaction and an activation reaction. Often, these reactions have to be performed at many sites on the same molecule simultaneously. The first method introduced was "Divergent Growth" by Tomalia[6,16] in which dendrimer is originated from a core. In this route dendrimer grows outward from a core to surface. The second method, pioneered by Hawker and Fréchet[17] follows a "Convergent Growth", in which, several dendrons are prepared and reacted with a multifunctional core to obtain a dendrimer. So, a dendrimer grows inwards from surface to core. Over 100 compositionally different dendrimer families have been synthesized and over 1000 differentiated chemical surface modifications have been reported, mainly on the basis of these two synthetic routes[18-21].

Divergent route

In divergent approach, synthesis of dendrimer starts from a multi-functionalized initiator core (Figure 2), to which multi-functionalized branching units or monomers are attached in first step. During this reaction surface functionality of this branching units are deactivated or protected. After completion of first step these surface groups are activated or unprotected, which undergoes further reaction. These iterative reactions steps are repeated until desired generation of dendrimer is obtained and a dendrimer grows outwards from core to surface. Moreover, as the dendrimer grows larger, the end groups on the surface become more and more closely packed and because of steric hindrance, the dendrimer reaches its upper generation limit. This is known as the "de Gennes dense packing"[22] named after Pierre-Gilles de Gennes or "starburst effect" named after Tomalia[23].

Convergent route

Hawker and Fréchet[17] developed the convergent methodology, which assembles the macromolecule from the outside to finish at the core. Convergent growth

generally starts from surface unit which coupled with a monomer unit to give a dendron whose focal point is deactivated or protected (Figure 3). In the second step of reaction the focal point becomes activated for further reaction, and the dendron is grown inwards. At the end of the reaction these highly branched dendrons reacted to a multi functionalized core to give a dendrimer.

The dimensions of dendrimer growth are subject to limitations set by steric-hindrance during reaction of the dendrons at the periphery. However, steric hindrance at the reactive point prevents the preparation of high generations of dendrimers because the final macromolecule is synthesized by coupling two or more wedges, which themselves are highly sterically demanding.
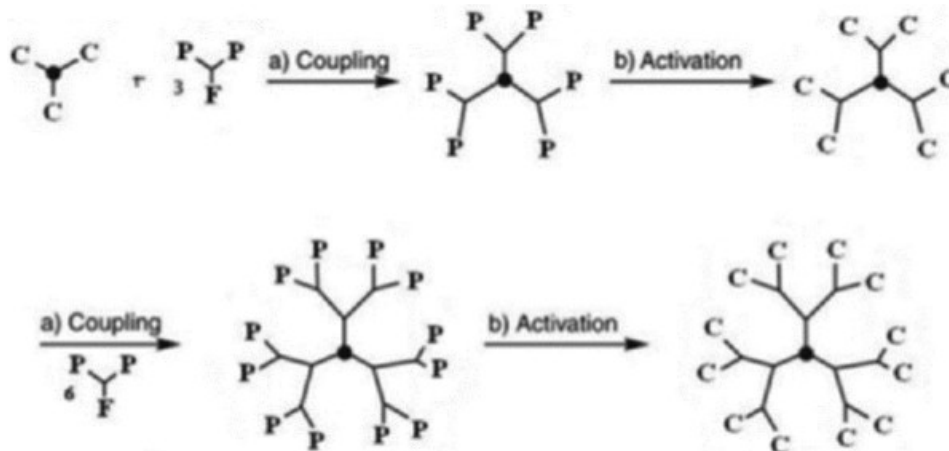

Figure 2 : Shows "Divergent Approach" (Where F=Unprotected functional group, P=Protected functional group and C=Coupling point)

Double exponential growth

The double-exponential method (Figure 4) can basically be regarded as a convergent growth strategy for a Dendron[24-26]. This approach involves growth of dendron in two directions:
1. Growth inwards towards core by focal point activation and
2. Growth towards surface by surface group activation.

A branching moiety containing two coupling sites both are completely protected undergoes selective deprotection. In two completely separate steps, branching unit in one step undergoes surface deprotection where as in other step it undergoes focal point deprotection. Now both unprotected dendrons are reacted in second step to give second generation dendron. Iteration of the synthetic sequence leads to the corresponding fourth-generation dendron.

Hypercore or hypermonomer approach

Frechet et al.[27] focused on acceleration of dendrimer synthesis. The outcome of this research was "Hypercores" approach. These methods involve the pre assembly of olingomeric species, which can then be linked together to give dendrimers in fewer steps or higher yields, taking advantage of the best points of both the convergent and the divergent technique. The "Hypercore" and "Branched Monomer" are pre-branched analogues of the cores and dendrons that are used in "Traditional" dendrimer syntheses.

Figure 5 shows how they could be utilized in the synthesis of large dendritic structures. The wedge is constructed by reaction of a surface unit with a branched monomer in one step followed by focal point activation in second step. Hypercore is constructed by divergent growth of core in single step. These surface activated hypercore and focal point activated wedge can be reacted in a single step to give fourth generation dendrimer.

Orthogonal coupling strategy

In an orthogonal synthesis two different branching units with complementary coupling functions are used alternating and no activation step is employed[28,29]. The selected reactants as well as the resulting coupling product must be inert towards the subsequent reaction conditions. The term orthogonal means that the functionalities are initially inert towards the coupling conditions, but can be activated *in situ* for the desired subsequent reaction or coupling.
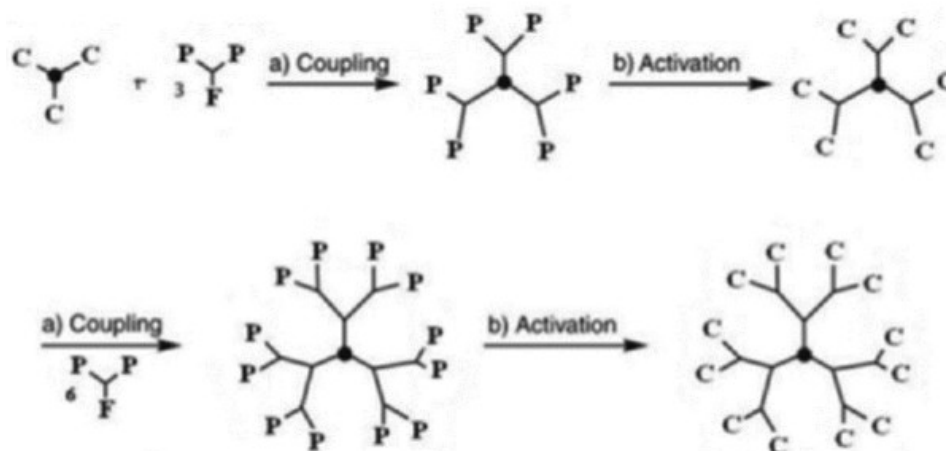
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Figure 3 : Shows "Convergent Approach" (Where C=Coupling point, P= Protected focal point and F=Unprotected or activated focal point)
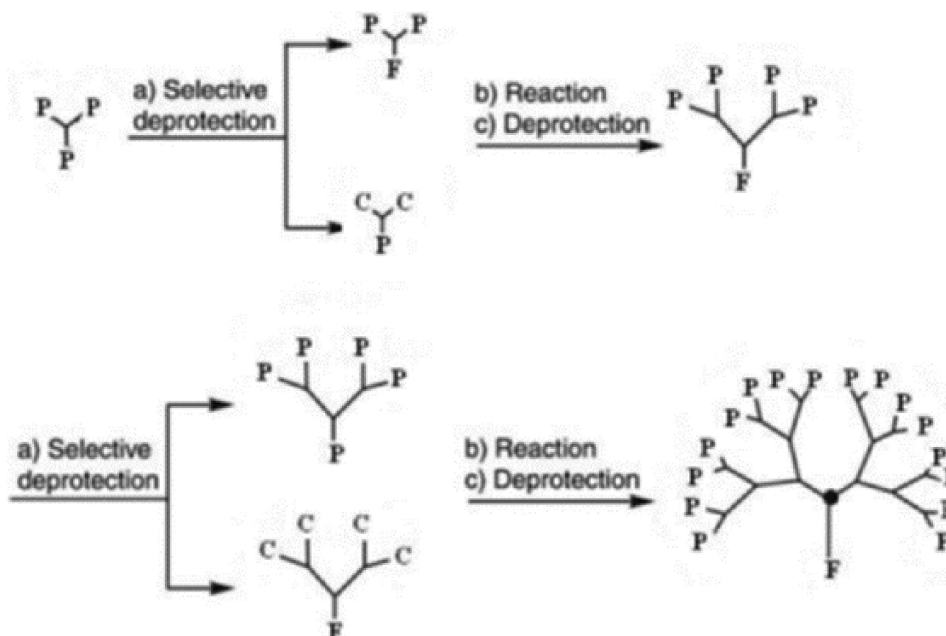

Figure 4 : Shows "Double Exponential Growth" (Where C=Coupling group, F=Functional group, and P=Protected group)

As shown in Figure 6, If this conditions are met, a dendrimer can be constructed either by divergent or convergent method in just a few steps.

However, the method of orthogonal coupling has still not been very widely adopted because the building blocks used have to meet very stringent structural requirements[30]. Spindler and Fréchet[28] were the first to prepare a third-generation polyethercarbamate dendron in a one-pot synthesis. Zeng and Zimmerman[31] reported the first application of orthogonal coupling to the synthesis of higher generation dendrimer. Freeman and Frechet[32] reported convergent synthesis of poly (benzyl ester) dendrimer and Shimanek et al.[33] reported synthesis of melamine based dendrimer by using or-

thogonal coupling strategy.

An advantage of such method is that it does not involve protecting group manipulations and functional group interconversions.

Lego chemistry

In "Lego chemistry" strategy, highly functionalized cores and branched monomers are applied to prepare phosphorus dendrimers. The end groups are generally phosphines and hydrazines. Generation 4 is synthesized in only 4 Steps and no. surface group increases from 48 to 250. This synthesis requires minimum volume of solvent, allow facile purification and produce environmentally benign by products such as water and nitrogen[34].
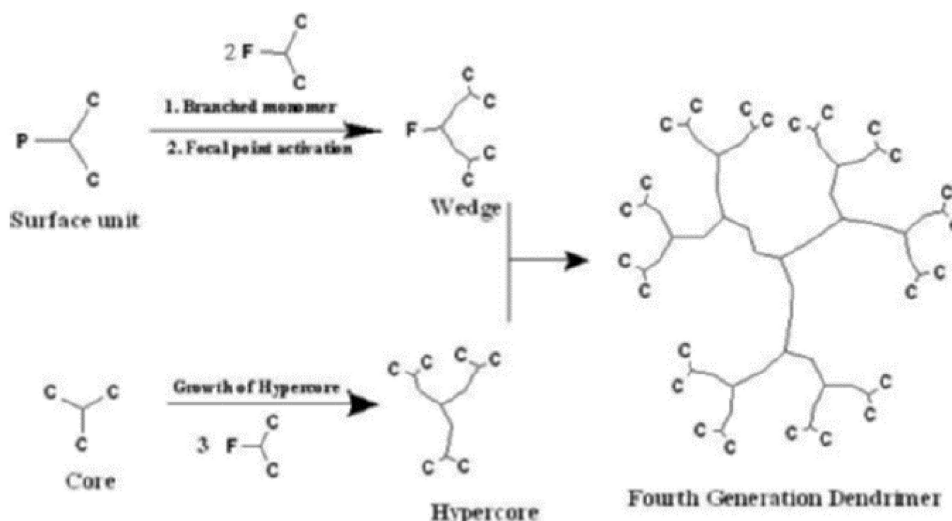
Figure 5 : Shows "Hypercores" or "Branched Monomers" Growth (Where C= Functional Group, F=Activated focal Point and P=Protected focal point)
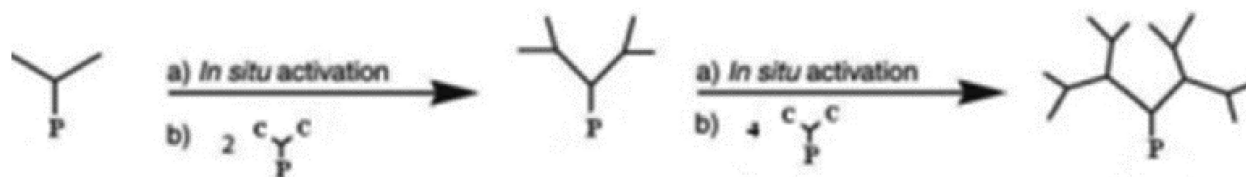

Figure 6 : Shows "Orthogonal Coupling Strategy" (Where P=Protecting group which on *in situ* activation is converted into C=Functional group which spontaneously undergoes Reaction)

Click chemistry

In 2001, Sharpless et al.[35] proposed this method in which smaller units are joined together by way of heteroatom bonds as a fast track route to compounds. Typical reactions applied are 1,3-dipolar cycloadditions, nucleophilic substitutions for ring opening of strained electrophilic heterocycles, as well as additions to carbon-carbon multiple bonds e.g. epoxidation. Azide functionalized PAMAM dendrons were produced by convergent method using click chemistry[36].

APPLICATIONS OF DENDRIMER

Dendrimer as carrier for drug delivery

Dendrimers led several groups to investigate the possibility of encapsulating drug molecules within the branches of a dendrimer. This offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability and controlling its release. Nature of drug binding may be either physical encapsulation into internal cavities of dendrimer or may be co-valent bond formation to the periphery of

dendrimer[37,38].

Dendrimers in ocular drug delivery

Anatomy and physiology of eye make it a very delicate and highly important organ. Designing an effective therapy for ocular diseases particularly for posterior region has considered a formidable task[39]. Eye contains various types of barriers such as different layers of cornea, sclera and retina including blood aqueous and blood–retinal barriers, choroidal and conjunctival blood flow etc. These barriers cause a significant challenge for delivery of a drug alone or in a dosage form, especially to the posterior segment of the eye[40]. The nano-size, ease of preparation, functionalization, and possibility to attach multiple surface groups renders dendrimers as suitable alternative vehicle of ophthalmic drug delivery[41-43]. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using poly(amidoamine) dendrimers with carboxylic or hydroxyl surface groups[44]. These surface-modified dendrimers were predicted to enhance pilocarpine & tropicamide bioavailability[45]. Also some of the phosphorus containing dendrimers with quaternary ammo-

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nium core and terminal carboxylic groups has successfully reported for ocular drug delivery of carteolol[46]. Yao et al.[47] have prepared and characterized the complex of puerarin and poly(amidoamine) (PAMAM) dendrimers and to evaluate the complex as an ocular drug delivery system. The results showed that puerarin-dendrimer complexes formed primarily by hydrogen-bonding interactions. Typically, 43, 56, 125, and 170 molecules of puerarin could be incorporated into G3.5, G4, G4.5, and G5 PAMAM dendrimer molecule. Puerarin was released more slowly from puerarin-dendrimer complexes than free puerarin in deionized water and phosphate buffer solution (pH 6.8). Furthermore, puerarin-dendrimer complexes produced longer ocular residence times compared with puerarin eye drops. No damages to the epithelium or endothelium were observed after the PAMAM dendrimer administration in this corneal permeation study. These results indicate that dendrimers are potential carriers for ophthalmic drug delivery.

Dendrimer in transdermal drug delivery

Transdermal drug delivery has made an important contribution to medical practice, but yet to fully achieve it's potential as an alternative to oral delivery and hypodermic injections[48]. A way to improve transdermal drug delivery is to use transdermal enhancers which increase permeation through skin. Therefore, polymeric enhancers with hydrophilic and hydrophobic groups like PAMAM dendrimers have attracted increasing interest. Wang et al.[49] reported the utilization of polyhydroxyalkanoate (PHA) and G3 PAMAM dendrimer as novel transdermal drug delivery systems. Tamsulosin hydrochloride was utilised as model drug and it was concluded that PHA-dendrimer matrix can be utilised as drug delivery systems. Yiyun et al.[50] reported that Poly(amidoamine) dendrimer complex with Non-steroidal Anti-inflammatory Drugs (NSAIDs) e.g. Ketoprofen, Diflunisal could be improving the drug permeation through the skin as penetration enhancers. Ketoprofen and Diflunisal were conjugated with G5 Poly (amidoamine) dendrimer and showed 3.4 and 3.2 times higher permeation. Chauhan et al.[51] investigated enhanced bioavailability of Poly(amidoamine)(PAMAM) dendrimer by using indomethacin as the model drug in transdermal drug delivery. Borowska et al.[52] have as-

sessed the ability of (PAMAM) dendrimers G3 and G4 to facilitate transdermal delivery of 8-methoxypsoralen (8-MOP) *in vivo*. *In vitro* study using Franz diffusion cell revealed an enhanced transdermal flux for 8-MOP in complex with G3 and G4 dendrimer in relation to standard 8-MOP solution.

Dendrimer in oral drug delivery

Oral drug-delivery system has been the dominant route for many years because of its significant advantages. It is by far the most convenient administration route with good patient compliance. Along with these benefits, there are also some defects of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes[53]. An ideal macromolecular carrier for orally administrated drugs should have the ability to protect the drugs from degrading. They might reduce nonspecific interactions with food proteins and allow enhanced absorption across the intestinal epithelium[9]. Duncan et al.[54] systematically investigated the effect of dendrimer size, charge and concentration on uptake by the adult rat intestine and studied the absorption mechanisms of dendrimers in intestine tissues so as to develop PAMAM dendrimers as potential oral drug carriers. It was suggested that dendrimer size was a key factor on determining overall uptake[55]. Oral drug delivery studies using the human colon adeno carcinoma cell line (Caco-2) have indicated that low-generation PAMAM dendrimer across cell membranes, presumably through a combination of processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the P-Glyco protein (Pgp) efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter[56]. But with increase in the concentration and generation, there was increase in the cytotoxicity and permeation of dendrimers. Ke et al.[57] developed a drug–PAMAM complex for oral administration. Doxorubicin was loaded into PAMAM, the cellular uptake and pharmacokinetics of the doxorubicin–PAMAM complex was studied. As the results, the cellular uptake of doxorubicin in Caco-2 cells treated with the doxorubicin–PAMAM complex was increased significantly with an increase in concentration and time, as compared to that treated with free doxorubicin. And the transport effi-

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ciency of the doxorubicin–PAMAM complex from the mucosal side to the serosal side was 4–7 times higher than that of free doxorubicin in different segments of small intestines of rat. The doxorubicin–PAMAM complex led to the bioavailability that was more than 200-fold higher than that of free doxorubicin after oral administration. These results indicate that PAMAM dendrimer is a promising novel carrier to enhance the oral bioavailability of drug, especially for the P-glycoprotein (P-gp) substrates.

Dendrimer in pulmonary drug delivery

The ability to deliver proteins and peptides to the systemic circulation by inhalation has contributed to a rise in the number of inhalation therapies under investigation. For most of these therapies, aerosols are designed to comprise small spherical droplets or particles suitable for particle penetration into the airways or lung periphery. Studies performed primarily with liquid aerosols have shown that these characteristics of inhaled aerosols lead to optimal therapeutic effect. Though still inefficient drug delivery can still arise, owing to excessive particle aggregation in an inhaler, deposition in the mouth and throat, and overly rapid particle removal from the lungs by mucocilliary or phagocytic clearance mechanisms. To address these problems, particle surface chemistry and surface roughness are traditionally manipulated[58]. During one study, efficacy of PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin was studied by measuring plasma anti-factor (Xa) activity, and by observing prevention efficacy of deep vein thrombosis in a rodent model. G2 and G3 generation positively charged Poly (amidoamine) dendrimers increased the relative bioavailability of Enoxaparin by 40%, while G2.5 PAMAM half generation dendrimers, containing negatively charged carboxylic groups had no effect. Formulations did not adversely affect mucociliary transport rate or produce extensive damage to the lungs. So, the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery[59]. The absorption-enhancing effects of poly amidoamine (PAMAM) dendrimers with various generations i.e. G0–G3 and concentrations i.e. 0.1%–1.0% (w/v) on the pulmonary absorption of peptide and protein drugs were studied in rats[60]. Insulin and calcitonin were chosen as models of peptide and pro-

tein drugs, and their pulmonary absorption with or without PAMAM dendrimers was examined by *in vivo* pulmonary absorption studies. PAMAM dendrimers significantly increased the pulmonary absorption of insulin and calcitonin in rats, and their absorption-enhancing effects were generation dependent. The adsorption-enhancing effects were increased with increase in generations. For the same generation, the absorption-enhancing effects of PAMAM dendrimers were shown to be concentration dependent. Dendrimers did not cause any membrane damage to the lung tissues. So, dendrimers are promising polymers for pulmonary drug delivery.

Dendrimers in controlled release drug delivery

Controlled release drug delivery is a new way to treat illnesses. The term controlled release refers to the ability of a drug delivery system to release a drug over an extended period of time at a controlled rate. It generally involves implanting an engineered polymer directly into the organ or system that is affected by a disase. Since the polymer is implanted directly into the tissues affected by disease, the side-effects are often small compared to systemic drug delivery. Dendrimers offer advantages including a lower polydispersity index, multiple sites of attachment, and a controllable, well-defined size and structure that can be easily modified to change the chemical properties of the system[61]. In addition, macromolecules such as dendrimers have an enhanced permeability and retention effect that allows them to target tumor cells more effectively than small molecules[62]. Liu et al.[63,64] have prepared poly (aryl-ether) dendrimers containing dual functionality on the surface. One is used to attach poly (ethylene glycol) (PEG) units on the surface to improve water solubility and the other one is utilized to attach hydrophobic drug molecules. They have also synthesized a series of dendritic uni-molecular micelles with a hydrophobic polyether core surrounded by a hydrophilic PEG shell for drug encapsulation. A third-generation micelle with indomethacin entrapped as model drug gives slow and sustained *in vitro* release, as compared to cellulose membrane control65. Poly (ethyleneglycol) PEG-2000 was conjugated to G3 Poly (amidoamine) (PAMAM) withvarying degree of substitution. Methotrexate drug was encapsulated to the prepared conjugates and in-

vestigated for drug release in a dialysis bag. The results found that PEG dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to no encapsulated drug. Asthana et al.[66] achieved controlled release of the Flurbiprofen by formation of complex with amine terminated G4 PAMAM dendrimers. Prepared dendrimer complexes observed that loaded drug displayed initial rapid release (more that 40% till 3rd hour) followed by slow release. Pharmacodynamic study was performed using carrageenan induced pawedema model, revealed 75% inhibition at 4th hour that was maintained above 50% till 8th hour. The dendritic formulation showed 2-fold and 3-fold increase in mean residence time and terminal half-life, respectively, as compared to free drugs. The results show potential of dendrimers in controlled release drug delivery.

Dendrimer in targeted drug delivery & cancer research

The application of drug carrier systems for targeting tumor cells has gained importance as an alternative approach for treating cancer and offers both increased therapeutic index and decreased drug resistance. Thereby increasing efficacy and reducing side effects of chemotherapy. An effective targeting drug-delivery system requires a base that is uniform and able to couple multiple components such as targeting molecule, drug and cancer imaging agent[67]. Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid. Membrane associated high-affinity folate receptors are folate-binding proteins that are over expressed on the surface of different types of cancer cells e.g. ovarian. Choi et al.[68] produce dendrimers conjugated to different biofunctional moieties like fluorescein and folic acid, and then link them together using complementary DNA oligonucleotides to produce clustered molecules that cancer cells that overexpress the high affinity folate receptor. These conjugates were injected i.e. into immuno deficient mice bearing human KB tumors that overexpress the folic acid receptor. These folate-conjugated nanoparticles concentrated in the tumor and liver tissue over 4 days after administration. Targeting methotrexate increased its antitumor activity and markedly

decreased its toxicity, allowing therapeutic responses which are not possible with a free drug. Patri et al.[69] have investigated that complexing a drug with dendrimer as an inclusion complex improves its solubility in water, a cleavable, while covalently linked dendrimer conjugate is better for targeted drug delivery because it does not release the drug prematurely in biological conditions. They reported less cytotoxic effect with the covalently linked dendrimer. Sharma et al.[70] studied synthesis of a surface modified dendrimer for cancer targeted drug delivery system. For this, G4 PAMAM dendrimer was conjugated with Gallic acid and characterized through UV, IR, 1H-NMR and mass spectroscopy. Cytotoxicity study of dendrimer conjugate was carried out against MCF-7 breast cancer cell line using MTT assay. The study revealed that the conjugate is active against MCF-7 cell line and might act synergistically with anti-cancer drug and gallic acid–dendrimer conjugate might be a promising nano-platform for cancer targeting and cancer diagnosis.

Dendrimer in gene delivery

Dendrimers have unique molecular architectures and properties that make them attractive materials for the development of nano-medicines. Key properties such as defined architecture and a high ratio of multivalent surface moieties to molecular volume also make these nanoscaled materials highly interesting for the development of synthetic (non-viral) vectors for therapeutic nucleic acids[14]. Besides of that some research recently indicated that dendrimer based gene delivery system also have significant potential in clinical trials. Kukowska-Latallo et al.[71] reported that intravenous administration of G9 Poly(amidoamine) (PAMAM) dendrimer-complexed pCF1CAT plasmid could result in high level of gene expression in the lung tissues of rats. It enhances the transfection efficiency and expression pattern of dendrimers. Joester et al.[72] synthesized amphiphilic dendrimers having a rigid diphenylethyne core featured a variety of geometries and substitution patterns, all of which showed high transfection activity. The hydrophobic parameters influenced the DNA binding and transport more strongly than anticipated, exhibiting lower toxicity. In contrast to cationic dendrimers, these dendrimers did not have any size limitation for transfection. In another study; Takahashi et al.[73] syn-

thesized amphiphilic, PAMAM dendrimers of generations 1 to 4, and utilizing di-n-dodecylamine as the core. These complexes with DNA and, in case of the G 2–4 dendrimers, were able to cross cell membranes and efficiently deliver DNA. Huang et al.[74] conjugated ligand Transferrin with PAMAM dendrimer using bifunctional polyethylene glycol. This vector showed 2.25 fold increases in gene transfection compared with PAMAM and PAMAM-PEG *in vivo*. Yu et al.[75] introduced histidine residues into L-arginine grafted PAMAM G4 dendrimers to enhance proton buffering capacity and evaluated the physicochemical characteristics and transfection efficacies *in vitro*. The results showed that the synthesized PAMAM G4 derivatives effectively delivered p-DNA (plasmid DNA) inside cells and the transfection level improved considerably as the number of histidine residues increases.

Dendrimers in catalysis

The combination of high surface area and high solubility makes dendrimer useful as nanoscale catalysts[76]. They combine the advantages of both homogenous and heterogeneous catalysts. Homogenous catalysts are effective due to a good accessibility of active sites but they are often difficult to separate from the reaction stream. Heterogeneous catalysts are easy to separate from the reaction mixture but the kinetics of the reaction is limited mass transport. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra-filtration methods. The first example of a catalytic silane dendrimer was described by the group of Van Koten[77].

Bhyrappa et al.[78] developed a series of oxidatively robust Poly (phenylesters) dendrimers were through a convergent synthesis. Significantly greater regioselectivity is observed with the dendrimer metalloporphyrins, relative to the corresponding parent 5,10,15,20-tetraphenylporphyrinato manganese (III) cation.

In metallodendrimer, heterogeneous catalysis are a nickel-containing dendrimer are also reported active in the Kharasch Addition[77], palladium-containing dendrimers active in ethylene polymerization[79] and in the Heck Reaction[80].

Karakhanov et al.[81] developed Bimetallic Cu(II) and Pd(II) metal complexes with nitrile-based

dendrimers demonstrated high activity in Wacker Oxidation of terminal alkenes along with good selectivity for methylketone formation and same group has developed new heterogeneous catalysts based on Pd nanoparticles and cross-linked poly(propylene-imine) and poly(amidoamine) dendrimers were prepared and examined for selective hydrogenation of unsaturated compounds.

Rajesh Krishnan et al.[82] used poly (amidoamide) dendrimers as organo-catalysts for "Knoevenagel" and "Mannich" reactions in water. Knoevenagel Condensation between carbonyl compounds and active methylene compounds as well as three component Mannich reaction between aldehydes, ketones and amines proceeded smoothly in water with good to excellent yield and high selectivity in the presence of zero and first generation poly (amidoamine) dendrimer.

Dendrimer as membranes

Dendrimer with high degree of branching units, high density of surface functional groups, nano-scaled size, well-defined molecular weight and low-dispersity are suitable as membranes. Proton exchange membrane fuel cell (PEMFC) is believed to be the best type of fuel cell as a new clean and high efficient power, which will eventually replace the gasoline and diesel internal combustion engines. The function of the proton exchange membrane (PEM) is use to conduct the protons and separate the catalyst. Lee et al.[83] employed PAMAM dendrimers as components of PEM for fuel cells. Compared to the traditional "Nafion117", the membrane containing PAMAM dendrimers has higher proton conductivity but lower fuel permeability even under low humidity condition and or at high temperatures. Bipolar membrane is a type of composition membrane, which contains a cation-exchanging layer, an anion exchanging layer and an interfacial layer. The novel property of a bipolar membrane is that the water molecules can be dissociated efficiently into the hydrogen ions and hydroxyl ions under reverse potential bias. To improve the water dissociation ability of a bipolar membrane, PAMAM dendrimers were used as catalysts of the water dissociation process in the intermediate layer of a bipolar membrane by Fu et al[84]. They prepared the new bipolar membrane by immersing the heterogeneous anion exchanging mem-

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brane into Poly (amidoamine) (PAMAM) dendrimer aqueous solutions and casting the N,N-dimethylformamide (DMF) solution of sulphonated poly(phenylene oxide) (SPPO) onto the dendrimer treated anion exchanging membrane.

Sarkar et al.[85] reported first use of dendrimer in the modification of reverse osmosis (RO) membranes. The effects of dendrimer surface coatings on the advancing water contact angle i.e., coatings' hydrophilicity, permeate flux and % salt rejection of commercial polyamide membranes were studied. The membranes were coated by *in situ* crosslinking of amine-functional polyamidoamine (PAMAM) dendrimers and PAMAM–polyethylene glycol (PAMAM–PEG) multi-arm stars with difunctional PEG crosslinkers. The resulting coatings significantly reduced contact angles of membrane surfaces without affecting their % salt rejection and only moderately reducing their permeate fluxes. Lower contact angles indicated more hydrophilic membranes with the potential for increased resistance to fouling by hydrophobic foulants, such as biofoulants and organic pollutants.

CONCLUSION

Dendrimers have emerged as a real force to be reckoned with in chemistry. The large body of research on the synthesis of dendrimers shows how the different methodologies that have been developed can be applied to a wide variety of chemical systems. The techniques for the synthesis of dendrimers include methods in which structural and functional groups can be incorporated into a dendrimer in specific positions, potentially giving the chemist an extremely high degree of control over architecture, and functionality. Many researchers of multidisciplinary classes are working in the field of dendrimers towards variety of objectives which leads to several applications of dendrimer which are discussed herein. As progress in dendrimer synthesis will be more prevalent, there will be high level control over dendritic architecture as a result number of dendrimer classes will be expand and more number of applications will be prevalent. Still, lots of work is required done with respect to cost effectiveness for successful commercialization of this technology.

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