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Review Article

Dendrimers and their Applications

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ABSTRACT

Dendrimers are the valuable additives in different routes of drug administration and are the most successful agents, because dendrimers provide greater biocompatibility, water solubility and bioavailability. In this review, synthesis structures, method of preparation have been discussed. Interaction mechanisms between dendrimer molecules and active pharmaceutical ingredient (API), like simple encapsulation and covalent conjugation and the recent applications of dendrimers have also been focused. Divergent method of poly amidoamine (PAMAM) dendrimers is found to be more applicable as compare to convergent method and PAMAM are also considered as ideal carriers for drug delivery because of large variety of surface groups, high aqueous solubility, and their unique architecture.

Keywords: Dendrimer; PAMAM; PPI;

INTRODUCTION:

Dendrimer is derived from the Greek word "dendron" which is used for tree and from the Greek suffix "mer" (segment) which describes the synthetic, three-dimensional molecules having branching parts. Tomalia Donald and his co-workers discovered dendrimers in early 1980's for the first time. (Tomalia *et al.*, 1985).

Dendrimers are like tree shape artificial macromolecules. They are mono-disperse and three-dimensional and hyper-branched molecules, having property of host–guest entrapment and defined molecular weights.(Tomalia *et al.*, 1985). Dendrimers are prepared from branched monomer units in a step by step manner and it is possible to control their shape, dimension, molecular size, flexibility, density and solubility by choosing surface functional groups anddifferent building/branching units. (Tomalia *et al.*, 1990) Moreover, they can also possess polymers and organic molecules as a part of their structure, and thus acquire special chemical and physical properties.

Till now, dendrimers have been used in many fields, such as electrochemistry,(Credi *et al.*, 2004) photochemistry,(Momotake and Arai, 2004) and supra-molecular chemistry or host–guest chemistry (Al-Jamal *et al.*, 2005) , synthesis of nanoparticle,(Wu *et al.*, 2006) decolonization of dye (Cheng *et al.*, 2005) , pollution management , (Xu and Zhao, 2005) curing of epoxy resins, (Cheng *et al.*, 2007) catalysis, (Lee *et al.*, 1994) preparation of monomolecular membranes, (Sayed-Sweet *et al.*, 1997) delivery of drug, (Aulenta *et al.*, 2003, D'Emanuele and Attwood, 2005, Svenson and Tomalia, 2012) and transfection of gene. (Dufès *et al.*, 2005). In recent years, dendrimer's use in delivery systems acquired more attentions as compare to other fields.(Esfand and Tomalia, 2001, Gillies and Frechet, 2005).

Internal cavities/spaces are empty and open and often found in low-generation dendrimers, as a result they can encapsulate drug molecules which are hydrophobic in nature (Meijer, 1994).As compare to the conventional molecules they possess large number of functional groups at their surface. (Tomalia *et al.*, 1990). Solubility of drugs increases due to the presence of these functional groups in dendrimers. (Milhem *et al.*, 2000, Yiyun

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and Tongwen, 2005). Presence of large number of these functional groups on the surface of outer shell increases its reactivity, thus causing conjugation or modification of dendrimers with a chain of different guest molecules.(Yang *et al.*, 2004). Encapsulation of both the drugs and guest molecules can occur in the hydrophobic cavities of dendrimers or the conjugation with surface functional groups can occur. These properties are indicative that dendrimers are a suitable agent for delivery of drugs. Research is also being conducted in biomedical field for the application of dendrimers.

For the first three generations dendrimers resemble with ordinary organic molecules, as shown in Fig. 1. Dendrimers have no consistent or specific three-dimensional structure, instead they are small and floppy shaped in appearance. At generation 4 (G4), they appear to b spherical in shape. After G5 they show consistent and specific three dimensional structures. After G5 they become highly spherical in structure. (Singh *et al.*, 2008)

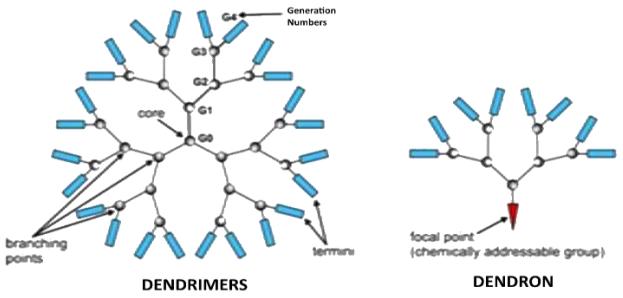


Figure: 1: Basic structure of dendrimer

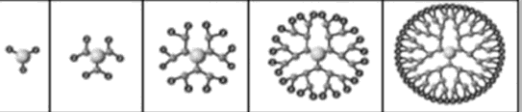
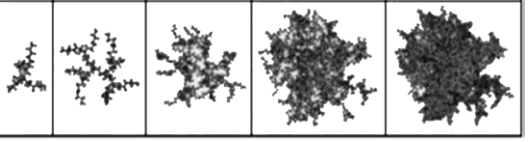
Dendrimers are branching molecules in nature and have a branch starting from the core. Depending on the core, dendrimer branches may be 3 and 4, which is the most common number. From the start of core, dendrimer shows atoms with long chains, possessing branching points after each half dozen atoms. The running chain of atoms then changes into two chains of atoms on each point of the branch. This type of molecular structure resembles with a tree having large number of branches. Dendrimer's diameter increases with the increase in generation number, similarly the surface group number also increases geometrically with increase in generation number as shown in Table 1.

STRUCTURES, SYNTHESIS, AND PROPERTIES OF DENDRIMERS

Structures of dendrimers

Usually, dendrimers are of two types of shapes i.e. globe shape and ellipsoid shape and they have three specific components, one is the central core,

Table 1: 2D and 3D representation of different dendritic generations

	G0	G1	G2	G3	G4
# of Surface Groups	3	6	12	24	48
Diameter (nm)	1.4	1.9	2.6	3.6	4.4
2D Graphical Representation					
3D Chemical Structure View					

second is repeated branch and third one are the functional groups on surface.(Aulenta *et al.*, 2003). On the central core, two functional groups are attached which are reactive in nature. Branches are arranged in concentric layers and are repeated radically, these layers are known as ''generations.' (G)'. Functional groups found at the surface of dendrimer' determine its physical properties in aqueous solutions or in solid state. Molecular weight, number of functional groups and dendrimer size , are associated with the generation of dendrimer and are controlled throughout the dendrimer synthesis.(Caminade *et al.*, 2005)

Synthesis of dendrimers

In general, two methods for production of dendrimers are used: first one is divergent method and the second is convergent method (Fig. 2)(Tomalia *et al.*, 1984). Tomalia in 1984, first of all published that divergent method is used for the synthesis of poly (amidoamine) (PAMAM) dendrimers. Later on, in 1990, Frechet and Hawker (Frechet, 1994) described the convergent method for synthesis of dendrimers. Convergent method make use of a top–down approach and starts from the margin of dendrimers while divergent one starts from the central core and widens in the direction of surface. Both methods have few advantages and disadvantages.

Divergent method has the ability to create high generation dendrimers. However, few defects are found on the surface of higher generation dendrimers as a result of steric resistance. Consequently, cleaning of the products after each repetitive series of preparation is necessary. As compare to divergent method, the convergent method have ease in characterization and purification, and have the potential of attracting Dendron's of different types to one dendrimer. (Mourey *et al.*, 1992).

At present, Polypropyleneimine (PPI) and PAMAM dendrimers are available in market and are commonly used in fields of biomedical sciences and can be synthesized only by the divergent method(Kim and Zimmerman, 1998). PAMAM dendrimers synthesis begins with Michael addition inside the middle core of multifunctional nature usually, ethylene diamine or ammonia and methyl acrylate. Three or four ester groups are found on the resulted product which is fully amidated with excess of ethylenediamine or ammonia and as a result molecules having three or four amine groups which are reactive in nature are formed. After repetition of the amidation reaction and Michael addition with a step-by-step manner, dendrimers of high-generation can be achieved. The products which have amine in the terminal as a functional group are referred to as ''full generation'' dendrimers denoted by G2, G3 and G4 as shown in Table 1.

After coming in contact with other groups like ester or carboxylate groups, they can be consider as ''half-generation'' dendrimers denoted by G2.5, G3.5 and G4.5. Commercially available dendrimers are (USA and Aldrich Chemical Company, Dendritech, USA and DSM Fine Chemicals, Austria) having trade mark like Starburst1. Other commercially available dendrimers of PPI dendrimer type (DSM Fine Chemicals and Aldrich), are prepared by divergent method, in which Michael addition occur stepwise in repeated manner among primary nitrile groups and amino groups (Dufès *et al.*, 2005). Commercially available dendrimers are now increasing day by day and are easily prepared by the divergent method in laboratory, but still it is a crucial challenge to synthesize dendrimers by means of the convergent method having fewer defects.

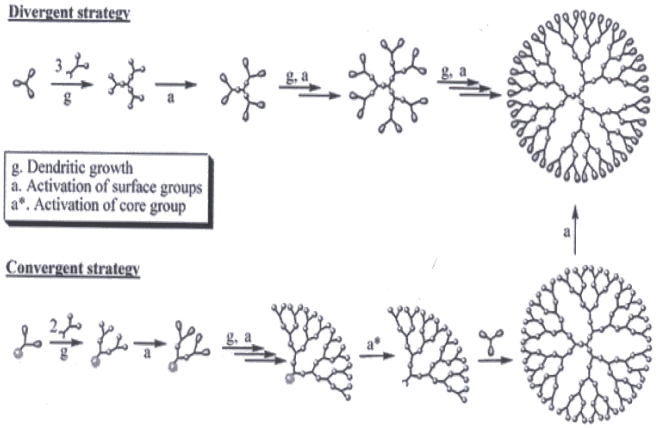


Figure 2: Divergent and the convergent methods for synthesis of dendrimers

Comparison of dendrimers verses linear polymers

Dendrimers are mono-dispersed macromolecules, as compare to the linear type polymers. Dendrimers often show considerably improved chemical and physical properties because of specific molecular architecture when we compare them with traditionally used linear polymers. Polymers having linear chain are usually found

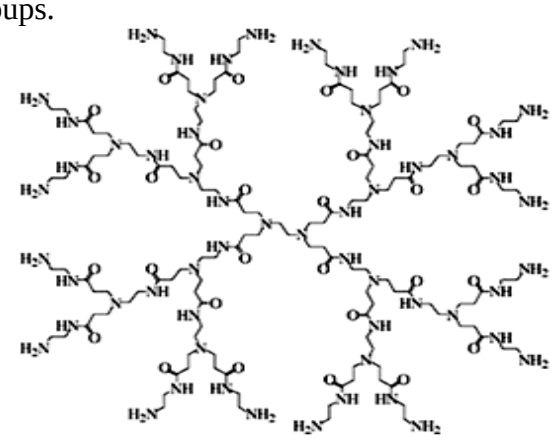
flexible coils while the rheological properties of dendrimers are affected because dendrimers form a very packed ball. Linear polymers have more viscosity than dendrimer solutions (Frechet, 1994). As the molecular mass increases in dendrimer, intrinsic viscosity also approaches to a highest level at generation 4 and then starts to decrease. This type of behavior differs from the linear polymers. In case of classical polymers, increase in molecular mass will increase the intrinsic viscosity continuously. (Mourey *et al.*, 1992).

Properties of dendrimers

Chain-ends present on dendrimers are responsible for miscibility, high reactivity and high solubility. The nature of surface groups affects the solubility of dendrimer. Because of having hydrophilic groups, solubility of dendrimers is greater in polar solvents, whereas those dendrimer which have hydrophobic groups show greater solubility in nonpolar solvents. The solubility of dendritic polyester is having higher solubility in tetrahydrofuran (THF) than that of analogous linear polyesters (Alper, 1991). Because of spherical shape of dendrimer and internal cavities, dendrimer possess defined properties. Possibility of encapsulating the molecules inside the macromolecule interior segments is very important property. Meijer and co-workers (Meijer, 1994) trapped p-nitrobenzoic acid/ rose bengal into the 'dendritic box' of poly-propylene imine dendrimers possessing about 64 branches on its corners.

TYPES OF DENDRIMERS

PAMAM or Poly-amidoamine were the first dendrimer which was commercialized and synthesized by the divergent" method in dendrimer family shown in Fig 3(a) (Esfand and Tomalia, 2001). PAMAM dendrimers structure starts from an ammonia (NH3) or ethylenediamine (C2H8N2) molecule as a core that binds to the amine (R-NH2) and amide (–CONH2R) group of branches (Frechet 1994, Silva Jr *et al.*, 2012). Size range of PAMAM dendrimers lies between 1.1 and 12.4nm as generations passes from 1–10 respectively. (Tomalia *et al.*, 1990). These dimensions have been compared with drug-polymer conjugates (5–20nm), viruses (25–240 nm) and proteins (3–8 nm). PAMAM are considered as ideal carriers for drug delivery because of large variety of surface groups.



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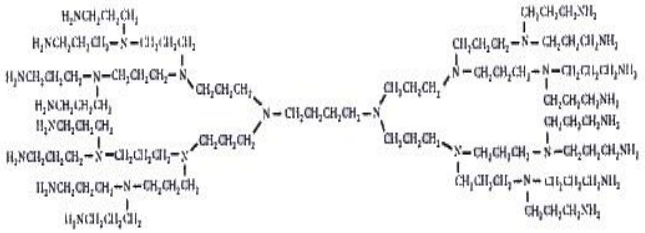

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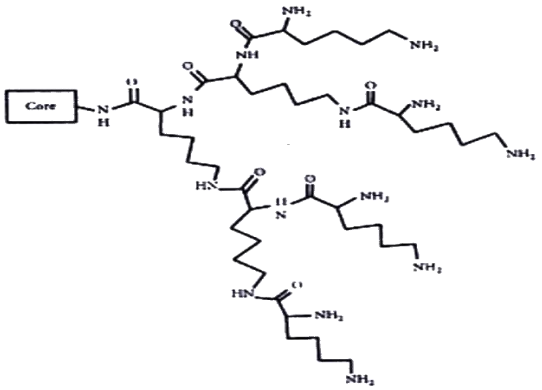

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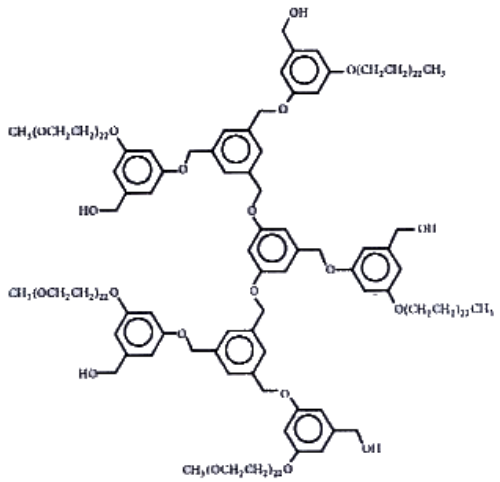

(d)

Figure 3: Types of dendrimers with structures: (a) PAMAM (b) poly-propyleneimine (c) polyaryl ether (d) biodegradable polylysine.

PAMAM was combined with silicon to form Poly (amidoamine) organosilicon (PAMAMOS) which were first commercial dendrimers which are inverted unimolecular micelles with exterior hydrophobic and interior hydrophilic polyamidoamine(Malik *et al.,* 2012).

Polypropyleneimine (PPI) dendrimers (Figure 3 (b)) have poly-alkyl amines also possessing primary amine groups at ends and up to 5th generation are commercially available. In previous literature, PPI were found to have significant toxicity due to presence of multiple cationic amine groups. (Malik *et al.,* 2000). In Polyaryl ether dendrimers (Figure 3 (c)) solubilizing groups are required at the periphery because of their poor water solubility for delivery of drugs(Liu *et al.,* 2000). In addition, biodegradable dendrimers have been designed which are based on polylysine (Figure 3 (d)), polyether, poly (disulfide amine), or polyester. After their surface modifications they have shown a promising antibacterial, antiviral, chemotherapeutic, and vaccine carrier candidates. Glycodendrimers, having carbohydrates and saccharide residue in their architecture, have great potential for being drug carriers. (Oliveira *et al.,* 2010). Amino acid-based dendrimers, hydrophobic dendrimers, peptide dendrimers, and asymmetric dendrimers were also investigated for a variety of pharmaceutical applications (Medina and El-Sayed, 2009).

*Several*dendrimer-based FDA approved products are available in the market. For example, Dade Behring (Stratus CS Acute Care), which contains dendrimer linked monoclonal antibody, it was launched for "cardiac diagnostic testing," similarly one of the product based on modified "Tomalia-type PAMAM" dendrimers, named as SuperFect (Qiagen), well-known gene transfection agent it is available for a wide range of cell lines (Challa *et al.,* 2011).

INTERACTION BETWEEN DENDRIMERS AND DRUG MOLECULES

End groups of dendrimers can be changed to obtain novel biological properties of molecules just like the cooperative receptor-ligand interactions, by which the dendrimers can interact with poorly soluble drugs. Dendrimers can also increase their cellular uptake, therapeutic efficacy, bioavailability and they can also be used to optimize the bio-distribution and systemic toxicity, clearance, and degradation rate of drugs can be reduced(D'Emanuele and Attwood, 2005).

Two methods are basically used for drug delivery by dendrimers: i.e. (1) lipophilic drugs being encapsulated inside hydrophobic dendrimer cavity to increase water solubility (2) Onto the surface of dendrimer, drugs can be covalently attached. In an encapsulation process drug is trapped inside the dendrimer by means of interaction between dendrimer and drug. The encapsulation may either involve nonbonding-specific interactions or a simple physical entrapment can occur inside the dendrimer. Drug can also attach to the exterior of the dendrimer in case of drug/dendrimer conjugates. These conjugates are usually pro-drugs that may be inactive or may have decreased activity. Covalent conjugation of the drugs is mainly used for achieving and targeting the higher drug payload, while the noncovalent interactions results in higher solubility of the insoluble drugs (Jain and Gupta, 2008). A basic schematic

representation of drug encapsulated and drug conjugated dendrimers is given in Figure 4.

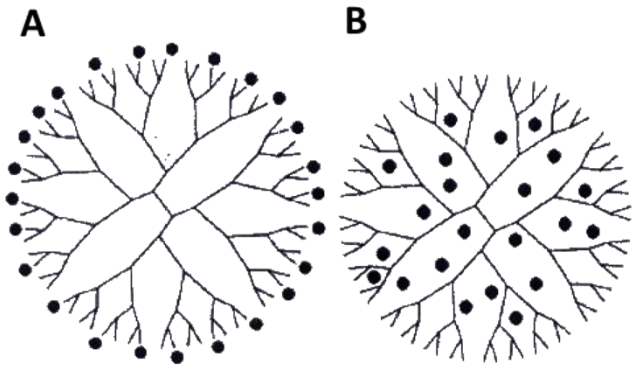

Figure 4: Schematic representation of drug conjugated (A) and drug encapsulated dendrimers (B).

1. ***Drug Encapsulation inside the Dendritic Structure.***

The acid-base reaction inside the dendrimers and guest molecules such as drugs with coulomb attractions causes the guest molecules to pull inside dendrimer structure, and keeps them together by hydrogen bonding. Jansen and coworkers reported the first encapsulation of a dye inside a dendrimer in 1994, the so-called "dendritic box"(Meijer, 1994). Into the dendritic cavities, guest molecules can be entrapped in the synthetic way, by means of preventing shell diffusion, after heating, sonication or solvent extraction.(Jansen *et al.,* 1995). After encapsulation of dyes to dendrimers, encapsulation of anticancer was the main focus of in research. Kojima and co-workers encapsulated anticancer drugs like doxorubicin and methotrexate using G3 and G4 ethylenediamine-based poly-amidoamine (PAMAM) dendrimers with poly(ethylene glycol) monomethyl ether (MPEG)grafts(Kojima *et al.,* 2000). Later on same group was also attached with methotrexate and folic acid to the exterior of the dendritic structure and was used to target the tumor cells by using drug-dendrimer conjugates(Kono *et al.,* 1999).Dendrimers with polar shell and an apolar core are called as "unimolecular micelles," and the dendritic structure not dependent on dendrimer concentration unlike conventional micelles(Stevelmans *et al.,* 1996). This approach has a disadvantage like the release of drugs from the dendrimer core is difficult to control.) Dendrimers can be changed by using Poly (ethylene glycol) by conjugating the dendrimer surface to PEG and produces a unimolecular micelle by providing hydrophilic shell on the dendritic core.

(Wendland and Zimmerman, 1999) prepared "cored dendrimers" having modified dendritic architecture to encapsulate the drug. after the synthesis, via cleavage of ester bonds core was removed, while the rest of the structure remained the same as a result of robust ether linkages (Schultz *et al.*, 2001).

2. Drug Dendrimer Conjugation.

The outer surfaces of dendrimers have many interaction sites with drugs so as to increase the loading capacity. With each higher generation of dendrimer, available surface groups increases in number for drug interactions increases in two folds. On dendritic systems, drugs are conjugated through amide, ester, or other linkage which depends on dendritic surface, that can be hydrolysed by lysosomal or endosomal enzymes, inside the cell (D'Emanuele and Attwood, 2005, Jain and Gupta, 2008).Many reports have revealed that free drug release can be increased through specific linkers in case of drug loaded dendrimer, particularly the flexibility and linker/spacer length. Few linkers are sensitive to pH-and proved to enhance free drug release in the intracellular region. (El Kazzouli *et al.,* 2012).

Patri *et al.* 2005 compared the covalently conjugated drugs and noncovalent inclusion complex in terms of efficacy and release kinetics, using generation 5 PAMAM dendrimers for targeting methotrexate. (Patri *et al.,* 2005). Covalent drug attachment using biodegradable linkages have a greater control over drug release than electrostatic drugs dendrimer complexes.

While the major disadvantage of the conjugation is the possibility of too slow drug liberation potential *in vivo*and less active release of drug. (Kaminskas *et al.,* 2012).

3. Dendritic Gels.

Hydrogels are "three-dimensional polymeric networks" having hydrophilic nature, they also have application in drug delivery because of their high water absorbing capacity(Hoare and Kohane 2008). "*In situ* forming gels" were also found to have a variety of applications including ocular, nasal, rectal, vaginal, oral, and injectable.(Navath *et al.,* 2011). Dendrimers and dendrons' with controlled sizes of molecules can be synthesized. This is because of their dendritic structure and this nature is between traditional gel polymers and the organic compounds with low molecular weight used in the "self-assembled supramolecular gels" (Smith, 2006). A "polymer network" is usually obtained with the use of a crosslinker during polymerization. Hydrogels synthesis is a function of the multivalent crosslinker behavior of dendritic molecules(Söntjens *et al.,* 2006).

APPLICATIONS

1. Dendrimers as a drug carrier

Dendrimers, due to their controllable size and mono-dispersity, can act as best carriers for large number of molecules, which are either encapsulated or makes interactions with the terminal groups of the dendrimer. The guest molecules, which are lipophilic, interact with the dendrimer core via Van der Waals or polar forces and are entrapped in its internal cavities. Dendrimers can be exploited as drug carriers for modifying drug properties that may include solubility enhancement, controlled release, drug protection, targeted drug delivery and many more.

1.1 Enhancement of Solubility

The trapping of a guest molecule inside the dendritic architecture or interaction with the terminal group's approaches can be used to change the solubility limitations of drugs having low solubility. Solubility enhancement of dendrimer mainly depends on different factors like: size of generation, concentration of dendrimer, core, pH, temperature effect, and terminal functionality. These factors are useful in increasing solubilization. Ionic interaction, hydrophobic interaction and hydrogen bonding are main mechanisms by which a dendrimer use their solubilizing property (Gupta *et al.,* 2006). Bhadra (Bhadra *et al.,* 2005) found that solubility of artemether can be enhanced up to three to fifteen times depending on the size of its generation, its concentration, and the type of micelles of MPEG (Methoxy polyethylene glycol) 2000 and 5000. Dendritic carriers were found by them for the formation of stable micelles at 10–30 *m*g/ml on the basis of MPEG type and generation.

1.2. Controlled release

Drug entrapment capability of dendritic nanostructures can be explored for controlled and/or sustained drug delivery. Various factors like dendritic generations, types of functional group within the dendrimer core, terminal functional group, nature and structure of host, pH, and temperature can affect the drug release from dendrimers. Kumar (Vijayaraj Kumar *et al.,* 2007) studied dendritic architecture of PEGylated poly (propylene imine) for anti-tuberculosis drug delivery like rifampicin. The drug loading capacity was increased by PEGylation of the system. This PEGylation reduced the release rate of drug and its hemolytic toxicity. For prolonged delivery of rifampicin, these were the suitable systems. Na et al. (Na *et al.,* 2006) came to know that polyamidoaminedendrimers possess the potential for carrying drugs like ketoprofen by both the *in vivo* and *in vitro* studies. *In vitro* release of ketoprofen from the complex of drug-dendrimer was extensively slow as compare to ketoprofen alone.

2. Dendrimers as vectors for delivery of genes

It was also found recently that efficient gene delivery can be mediated to a variety of cell types

by the use of dendrimers. Reports seen regarding the use of PAMAM and amino-terminated PPI dendrimers in the form of gene transfer agents which (non-viral), increasing the transfection of DNA endocytosis and, ultimately, into the cell nucleus (Eichman *et al.,* 2000). Protection of DNA from the action of DNAase which is present in serum includes in the advantage of dendrimers in *in vivo* studies. PAMAM dendrimers can carry of genetic material (Kukowska-Latallo *et al.,* 2000). These dendrimers are terminated at amino groups, which will interact the nucleic acids at their phosphate groups, resulting in development of transfection complexes. Commercially a transfection reagent known as Super-Fect TM having dendrimers in active form is also available. Activated dendrimers consist of genetic material which is in large quantity as compare to the viruses. Complexes of DNA named as Super Fect have the characteristic of having greater stability and an efficient source for DNA transport into the nucleus as compare to that of liposomes. In dendrimers, the transfection efficiency is found due to low pK and shape of the amines. Change in pH is buffered by this low pK value in the endosomal compartment (Haensler and Szoka Jr 1993)

3. Dendrimers as drugs

Anionic dendrimers have been shown to have antiviral activity. Having approximately the size of a virus, dendrimers are designed to bind multivalent either to the viral components or to the host cell surface through electrostatic forces, causing inhibition of infection at the stage of entry of virus to the cell. Dendrimer not only inhibit entry of virus but also inhibit its replication.(Gong *et al.,* 2002). Activity has been shown against HSV, RSV and HIV while Starpharma'sVivagelTM, a vaginal dendrimeric formulation against HIV is currently entering clinical trials phase II (Gong *et al.,* 2005). Dendrimers have also been shown to exhibit antimicrobial activity. Typically these dendrimers have cationic surface groups, usually lysine residues, which interact with the heavily negatively charged prokaryotic membranes destabilizing them, leading to lysis of the bacterial cell (Klajnert *et al.,* 2006).

4. Dendrimers in drug delivery

Nanoparticle drug-delivery systems have significant importance as they possess the ability to increase the stability and selectivity of the therapeutic agents. Drug-delivery systems containing dendrimer have been proposed in wide range. Encapsulation of guest molecules in the empty spaces inside the dendrimers interior is a common design (Figure 5a). One could also visualize dendrimer–drug networks (Figure 5b). Prodrugs, with therapeutic agent linked to a dendrimer surface (covalently or non-covalent interactions (Figure 5c) are also a target of active research (Esfand and Tomalia, 2001, Göller *et al.,* 2001). A dendrimer with hydrophobic-hydrophilic core-shell having interior of PAMAM and long chains of alkane on the exterior found to have the ability to bind with 5-flurouracil, which is anti-tumor drug and water-soluble in nature. Coating of the dendrimer fatty- acid macromolecule with phospholipid results in increase oral bioavailability of 5-flurouracil which was greater than that of 5-flurouracil in free form in case of rats (Tripathi *et al.,* 2002). Liposomal formulations including dendrimers entrapped and then they slowly release methotrexate (Khopade *et al.,* 2002).

(a)

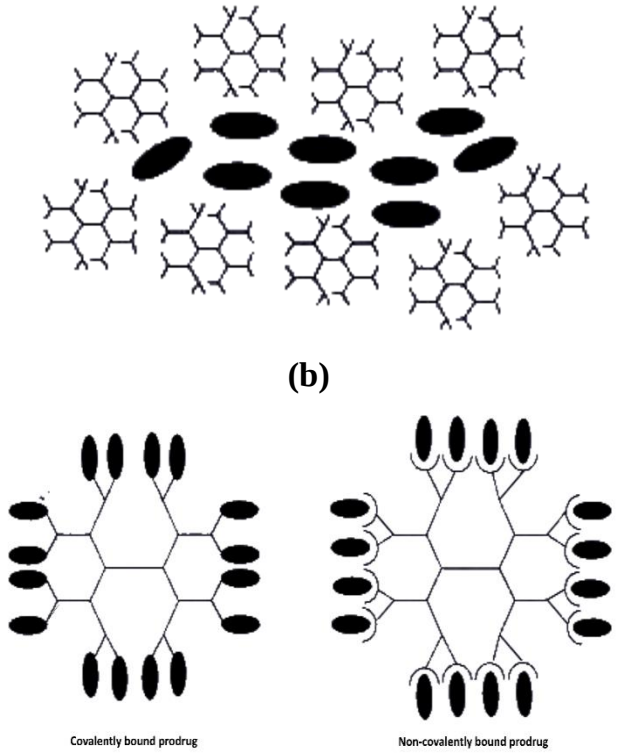

Figure 5: Dendrimer drug-delivery systems, a schematic view. The dark oval shows an active substance:
(a) Encavitated guest, (b) Dendrimer-drug networks, (c) Current Opinion in Chemical Biology.

Dendrimers with surface residues like saccharide can be used to direct a system to a target and then deliver covalently attached or complexed drugs. It should be noted that dendrimers developed for MRI include both imaging and targeting components (Konda *et al.,* 2002).

5. Dendrimers as diagnostic tools

Dendrimer technology provides a valuable methodological diagnostic tool, with applications in various bioassays and in the construction of contrast agents for imaging. Dendrimers are widely investigated as in the magnetic resonance imaging, they can be particularly designed to carry ionic contrast agents (Mn3þ Gd3þ, Mn2þ), by covalent interactions or by chelation while minimizing their toxicity and controlling their bio-distribution (Langereis *et al.,* 2006).Gadomer-17, was the first commercial dendrimer-based contrast agent which was developed by Schering AG, and have a polylysine-DTPA dendrimer along with Gd3þ ions on the periphery. Dendrimers are being used as tools for the increase of the sensitivity of the assays in microarray and ELISA bioassays, by enhancing the signal generation because of multivalent binding. Dendrislides TM from Genopole are dendrimer based DNA chips and are used for oligonucleotide detection and highly amplified labeling of PCR products for microarray detection.

6. Miscellaneous dendrimer applications

There are many other areas like biological chemistry where application of dendrimer systems can be helpful. For example, highly sensitive analytical devices (Yoon *et al.,* 2002) like MRI contrast agents (Konda *et al.,* 2002) burn treatment (Halkes *et al.,* 2002), prion research (Supattapone *et al.,* 2002) and EPR imaging with spin-labeled dendrimers(Yordanov *et al.,* 2001) are different areas of interesting ongoing dendrimers research that are further than the scope of this article.

CONCLUSION

Dendrimers have a bright future in different fields of applications pharmaceutical industries and also in diagnostic field in recent years because of having exceptional characteristics, such as high degree of branching, globular architecture, multivalence, and their molecular weight, therefore presenting them as a good candidate for drug delivery. Many drugs which are being developed today face the problems like poor solubility, permeability and bioavailability. Dendrimers are the best tool for increasing the delivery of such type of drugs. Toxicity and the biocompatibility problems can be controlled by surface engineering. Success has been achieved in simplification and optimization of the production of dendrimers with a wide range of structure having low expenditure of their manufacturing.

With the passage of progress in research, there will also emerge latest applications of dendrimers and number of drug delivery systems for dendrimers will be definitely increased on commercial level.

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