REVIEW ARTICLE

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A Path for Horizing Your Innovative Work

DENDRIMER: POLYMER OF 21ST CENTURY

VARUN TRIVEDI[1], UPENDRA PATEL[1], BHAVIN BHIMANI[1], DHIREN DASLANIYA[2], GHANSHYAM PATEL[2], BIJAL VYAS[3]

1. Arihant School of Pharmacy & BRI, Adalaj.

2. Department of Pharmacy, JJTU University, Jhunjhunu, Rajasthan.

3. Department of Pharmaceutics, Indubhai Patel College of Pharmacy and Research Centre, Dharmaj.

Corresponding Author Email: varun3838@yahoo.co.in

Abstract: The review aims majorly on four areas namely: Architecturing, Synthesis, Properties & Applications of the **dendrimer**. The unique architectural design of **dendrimers**, high degree of branching, multivalency, globular architecture and well-defined molecular weight, clearly distinguishes these structures as unique and optimum nanocarriers in medical applications such as drug delivery, gene transfection, tumor therapy, diagnostics, etc. Synthetic approaches lead to a dendritic architecture with properties amenable to modifications of shape, size, polarity, surface properties and internal structure. Nanoparticle drug-delivery systems are the popular ones as are able to increase the selectivity and stability of therapeutic agents. However reticuloendothelial system (RES) uptake, drug leakage, immunogenicity, hemolytic toxicity, cytotoxicity, hydrophobicity restrict the use of these nanostructures. These shortcomings are overcome by surface engineering the dendrimer such as Polyester dendrimer, Citric acid dendrimer, Arginine dendrimer, Glycodendrimers, PEGylated dendrimers, etc. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached i.e. conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. In addition to supplying a multivalent backbone for drug attachment, dendrimers also provide access to various new polymer architectures that are potentially relevant to drug delivery applications.

Keywords: Dendrimer, Nanotechnology, Nanoparticle

INTRODUCTION

In 1978, Fritz Vogtle and co-workers, introduced dendrimer chemistry[1] and in 1985, Donald A. Tomalia, synthesized the first family of dendrimers[2]. Dendrimers are repeatedly branched roughly spherical large molecules and possess well defined chemical structures[3]. The word dendrimer comes from a Greek word which means to "tree". At the same time, Newkome's group independently reported synthesis of similar macromolecules. They called them arborols from the Latin word 'arbor' also meaning a tree[4].The other synonyms for dendrimer include cascade molecules. It is a highly branched synthetic polymer and consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped or generational structure with precise molecular weights, diameters in the 2 to 10 nm range size, its unique architectural design, high degree of branching, multivalency, globular structure and representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". Poor solubility, bioavailability, permeability, biocompatibility and toxicity can be overcome by dendrimers. Recent successes in simplifying and optimizing the synthesis

of dendrimers provide a large variety of structures with reduced cost of their production. Dendritic polymers or dendrimers provide a route to create very well-defined nanostructures suitable for drug solubilisation applications, delivery of oligonucletide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral,

TYPES OF DENDRIMERS

(1) Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS)

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new

applications in nanolithography, lectronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honeycomblike networks with nanoscopic PAMAM and OS domains.[6,7]

(2) Poly (amidoamine) dendrimers (PAMAM)

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. When looking at the structure of the high-generation in two-dimensions, star like pattern observed. They are commercially available as methanol solutions and ingeneration G 0-10 with 5 different core type and 10 functional surface groups.[8, 9]

(3) Poly (Propylene Imine) dendrimers (PPI)

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary tris-propylene amines present in interior portion. It commercially available up to G5, and wide applications in material science as well as in biology.[10] PPI dendrimers are available as AstramolTM.

(4) Chiral dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches

to chiral core. Their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.

(5) Liquid crystalline dendrimers

A highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour. They consist of mesogenic (liq. crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers.

(6) Tecto dendrimer

Tecto Dendrimer are composed of a core dendrimer, perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

(7) Hybrid dendrimers

Hybrid dendrimers are hybrids (block or graft polymers) of dendritic and linear polymers. Obtained by complete monofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic selforganized lattices that are less readily available from other modified dendritic structures.

(8) Multilingual Dendrimers

Multilingual Dendrimers contains multiple copies of a particular functional group on the surface.

(9) Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

STRUCTURE OF DENDRIMERS

A dendrimer is typically symmetric around the core (fig1), and often develops a three-dimensional morphology .In the view of polymer chemistry dendrimeres are perfect monodisperse macro molecules with regular highly branched three dimensional structures (figure 2) and consist of three architectural components like core,branches and end groups.[12,13]

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure[14]. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the 'starburst effect[15]. For PAMAM dendrimer synthesis it is observed after tenth generation. The rate of reaction drops suddenly and further reactions of the end groups cannot occur. The tenth generation PAMAM contains 6141 monomer units and has a diameter of about 124 Å [16]

The increasing branch density with generation is also believed to have striking effects on the structure of dendrimers. They are characterised by the presence of internal cavities and by a large number of reactive end groups (Fig. 3). Dendritic copolymers are a specific group of dendrimers. There are two different types of copolymer.
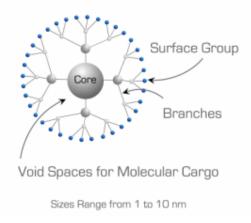
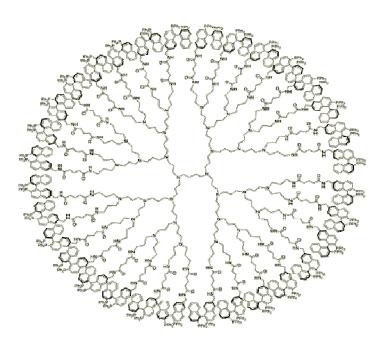Figure 1. Schematic representation if a generation 2 dendrimer

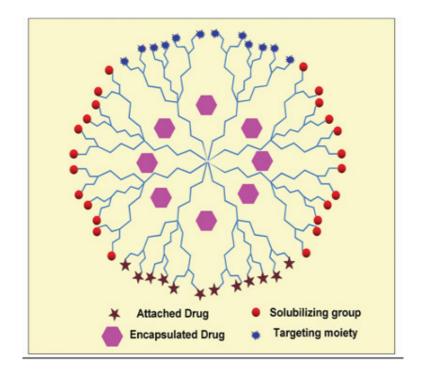Figure 2. Highly branched three dimensional structures

Figure 3. Dendritic box encapsulating guest molecules

Segment-block dendrimers

are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one polyfunctional core molecule.

Layer-block dendrimers consist of concentric spheres of differing chemistry. They are the result of placing concentric layers around the central core. Hawker and Fréchet[17] synthesised a segment- block dendrimer which had one ether-linked segment and two ester-linked segments. They also synthesised a layer-block dendrimer. The inner two generations were ester-linked and the outer three ether-linked. The multi-step synthesis of large

quantities of higher generation dendrimers requires a great effort. This was the reason why Zimmerman's group applied the concept of self-assembly to dendrimer synthesis[18]. They prepared a wedgelike molecule with adendritic tail in such a manner that six wedge-shaped subunits could self-assemble to form a cylindrical aggregate. This hexameric aggregate is about 9 nm in diameter and 2 nm thick. It has a large cavity in the centre. The six wedges are held together by hydrogen bonds between carboxylic acid groups and stabilised by Vander Waals interactions. However, the stability of the hexamer is affected by many factors. The aggregate starts to break up into monomers when the

solution is diluted, when the aggregate is placed in a polar solvent like tetrahydrofuran (THF), and when the temperature is high. The hexamer's limited stability is due to its noncovalent nature.

PROPERTIES OF DENDRITIC POLYMER

(1) Nanoscale sizes that have similar dimensions to important bio-building blocks, e.g., proteins, DNA.

(2) Lower generation anionic or neutral polar terminal surface groups show positive biocompatibility patterns as compared to higher generation neutral apolar and cationic surface groups.

(3) When dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) show nonor low-immunogenicity.

(4) Ability to arrange excretion mode from body, as a function of nanoscale diameter.

(5) An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties, reduces the drug toxicity and facilitates controlled release.

(6) Numbers of terminal surface groups suitable for bioconjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.

(7) Surfaces that may be designed with functional groups to resist trans-cellular, epithelial or vascular bio permeability.

(8) Optimize biodistribution, receptor mediated targeting, therapy dosage or controlled release of drug from the interior space after the modification of surface groups.

(9) Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers.

(10) Dendrimers are monodisperse macromolecules. Size and molecular mass of dendrimers can be specifically controlled during classical polymerization process.

(11) In solution, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solution has significantly lower viscosity than linear polymers. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline.

(12) Dendrimers have some unique properties because of their globular shape and the presence of internal cavities, to

encapsulate guest molecules in the macromolecule interior.

(13) The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Dendrimers solubility is strongly influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents[19, 20]

SYNTHESIS OF DENDRIMER

DRIMER

Mainly four methods are present for synthesis of dendrimers:

(1) Divergent growth method

This method was introduced by Tomalia. In this method growth of dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained. By this approach the first synthesized dendrimers were polyamidoamines (PAMAMs), also known as starbust dendrimers[21]

(2) Convergent Dendrimer Growth

Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.[22]

(3) Double Exponential and Mixed Growth

In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.[21, 22]

(4) Hypercores and Branched Monomers growth

This method involved the pre-assembly of oligomeric species which can be linked

together to give dendrimers in fewer steps or higher yields.

ENCAPSULATION OF DRUGS WITHIN THE DENDRITIC ARCHITECTURE

Dendritic architecture (open nature) has 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. The nature of drug encapsulation within a dendrimer may be simple physical entrapment, or can involve non-bonding interactions with specific structures within the Dendrimer.[23-25]

(1) Unimolecular micelles

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. For example synthesised a symmetrical, four directional saturated hydrocarbon cascade polymer containing 36 carboxylic acid moieties with a neopentyl core. It was shown that lipophilic probes were located within the lipophilic infrastructure of the dendritic structures and it was concluded that the polymers exist as single molecules capable

of molecular inclusion and therefore act as unimolecular micelles.[26-29]

(2) PEGylated dendrimers

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer to provide a hydrophilic shell around a hydrophobic dendritic core to form a unimolecular micelle. Because of its high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications. Liu et al., pentanol-based monomer was used to increase the flexibility and cavity size of the dendritic architecture by use of PEG.[30, 31]

(3) Dendritic box

Jansen et al. described the synthesis of poly (propyleneimine) dendrimers based dendritic boxes. During the synthetic process, guest molecules could be entrapped within the cavities of the dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication. Through end group modification with a bulky amino acid derivative to yield a dense and rigid

chiral shell with solid-phase properties and a flexible core capable of entrapping molecules[32, 33].

(4) Cored dendrimers

Zimmerman and co-workers synthesised cored dendrimers that resemble hollow nanospheres,encapsulate substances made them candidates for delivery vehicles. Encapsulation was achieved by postsynthetic modification of the dendritic architecture. The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups[34, 35].

SURFACE INTERACTIONS BETWEEN DRUGS AND DENDRIMER

The external surfaces of dendrimers have been investigated as potential sites of interaction with drugs. Although the number of guest molecules incorporated into a dendrimer may be dependent to a limited extent on the architecture of a dendrimer, the loading capacity may be dramatically increased by the formation of a complex with the large number of groups on the

dendrimer surface. The number of surface groups available for drug interactions doubles with each increasing generation of dendrimer.

(1) Electrostatic interaction between drug and

Dendrimer

The presence of large numbers of ionisable groups on the surface of dendrimers provides an interesting opportunity for electrostatic attachment of numerous ionizable drugs, providing the resultant complex retains sufficient water solubility. For example electrostatic interaction can occur between PAMAM dendrimers and nonsteroidal anti-inflammatory drug ibuprofen. Electrostatic interaction can occur between the carboxyl groups of this weakly acidic drug and the amine groups of the dendrimers. It has been estimated that approximately 40 ibuprofen molecules interact with G4 PAMAM dendrimer at pH 10.5 causing a considerable enhancement of drug solubility[36].

(2) Conjugation of drug to dendrimer

The covalent attachment of drugs to the surface groups of dendrimers through hydrolysable or biodegradable linkages offers the opportunity for a greater control over drug release. Yang and Lopina have

conjugated penicillin V (XII) with both G2.5 and G3 PAMAM dendrimers through a PEG spacer via amide and ester bonds, respectively. The use of an amide linkage provided bond stability, whereas ester linkage of the drug to the dendrimer provided a means of controlling drug release via hydrolysis. The microbial activity of the penicillin released by ester hydrolysis of the PEG-PAMAM (G3) conjugate was approximately the same (within 3%) as that of non-modified penicillin[37, 38].

APPLICATION OF DENDRIMER

1 Pharmaceutical application

1.1 Dendrimer in ocular drug delivery

Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable[38].Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability[38, 39].

1.2 Dendrimers in pulmonary drug delivery-

Dendrimers have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40 % [40].

1.3 Dendrimer in transdermal drug delivery-

Dendrimers designed to be highly watersoluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) could be improving the drug permeation through the skin as penetration enhancers [41]. Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. Chauhan et al. investigated enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application. (chauhan)[42]

1.4 Dendrimer in oral drug delivery-

Oral drug delivery studies using the human colon adenocarcinoma cell line, Caco-2,

have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the Pgp efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter[43]. As increase in the concentration and generation, there was increase in the cytotoxicity and permeation of dendrimers.

1.5 Dendrimers in targeted drug delivery

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 and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. DNAassembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics [44].

1.6 Dendrimers for controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into

PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construct involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5-fluorouracil. Encapsulation of 5-fluorouracil into G=4 PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. A third-generation dendritic unimolecular micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control[45].Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers[46]. The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to unencapsulated drug.

1.6 Dendrimers in gene delivery

Dendrimer-based transfection agents have become routine tools for many molecular and cell biologist's dendrimers are extensively used as non-viral vector for gene delivery. The use of dendrimers as gene transfect ion agents and drug-delivery devices have been extensively reviewed part[47]. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

1.7 Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behavior[48].

1.8 Cellular delivery using dendrimer carrier

Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake[49].

2 Therapeutic applications

2.1 Dendrimers in photodynamic therapy

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes[50]. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

2.2 Dendrimers for boron neutron capture therapy

Boron neutron capture therapy (BNCT) refers to the radiation generated from the capture reaction of low-energy thermal neutrons by 10B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. This radiation energy has been used successfully for the selective destruction of tissue.Dendrimers are a very fascinatingcompound for use as boron carriers due to their well defined structure and multivalency. The first example of a boroncontaining PAMAM dendrimer was synthesized by Barth et al[51].

3 Diagnostic applications

3.1 Dendrimers as molecular probes

Dendrimers are fascinating molecules to use as molecular probes because of their

distinct morphology and unique characteristics. For example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular probe, because of their large surface area and high density of surface functionalities [52]

3.2 Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools in medicine, and is applicable to numerous diseases. To obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent. Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Krause and co-workers synthesized a number of potential dendritic

X-ray contrast agents using various organo metallic complexes such as bismuth and tin[53, 54]

3.3 Dendrimers as MRI contrast agents

A number of research groups have explored the use of dendrimers as a new class of high molecular weight MRI contrast agents. Wiener and co-workers developed a series of Gd (III)–DTPA-based PAMAM dendrimers[55]. To improve the pharmacokinetic properties of dendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast agents have been considered. Wiener et al[56] synthesized a folate conjugated Gd (III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumour cells expressing the high affinity folateIJPR receptor.

Table 1.

Representative examples of nanocarrier-based drugs on the market

Compound	Commercial name	Nanocarrier	Indications
Daunorubicin	DaunoXome	Liposomes	Kaposi's sarcoma
Vincristine	Onco TC	Liposomes	Relapsed aggressive non-Hodgkin's lymphoma (NHL)
Paclitaxel	Abraxane	Albumin-bound paclitaxel	Metastatic breast cancenanoparticles

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