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DENDRIMERS - A NEW CLASS OF POLYMERS

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ABSTRACT: Dendrimers are highly branched and reactive three-dimensional macromolecules, with all bonds emanating from a central core. Compared with traditional linear polymers, Dendrimers have much more accurately controlled structures, with a globular shape, a single molecular weight rather than a distribution of molecular weights, and a large number of controllable 'peripheral' functionalities. All these versatile features of dendrimers have made their application in various areas like Biomimetic, Pharmaceutical drug delivery, Gene delivery, Chemotherapy and Diagnostics very attractive. This review briefly discusses different types of dendrimers with their structures and their methods preparations. We have emphasized on applications of dendrimers.

INTRODUCTION: Dendritic polymers are the fourth major architectural class of macromolecules. They represent a fourth major class after traditional types which includes;

1. Linear,
2. Cross-linked and;
3. Branched architectures

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Dendrimers have been referred to as "the polymers of the 21st Century." The structure of these materials has also a great impact on their applications. At the first time dendrimers were synthesized by Vögtle [1]. A 'cascade' synthesis was described, wherein an exhaustive Michael-type addition of acrylonitrile to an amine, followed by the reduction of the nitrile groups to primary amines, could theoretically be repeated infinitely to produce very highly branched macromolecular ligands.

Research groups led by Tomalia [2] and Denkewalter [3] devised routes whereby stepwise 'polymerizations' could be performed, giving highly branched polymers with extremely low polydispersities. At the same time, Newkome's group [4] independently reported synthesis of similar macromolecules. They called them *arborols* from the Latin word 'arbor' also meaning a tree.

The term *cascade molecule* is also used, but 'dendrimer' is the best established one. Dendrimers are a novel class of spheroid or globular nanoscaled macromolecules, characterized by highly branched tree like structures that provides a high degree of surface functionality and versatility. Their size ranges from 1 to over 10nm. The word "*dendrimer*" originated from two words, the Greek word *dendron*, meaning tree, and *meros*, meaning part.

Structure of Dendrimers: Basically, Dendrimers are spheroid or globular nanostructures that are precisely engineered to carry molecules encapsulated in their interior void spaces or attached to the surface (**Fig. 1**).

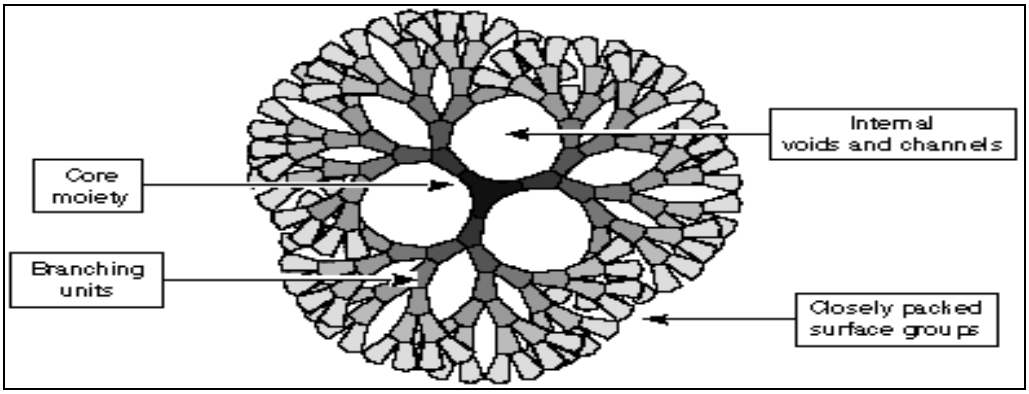

FIG. 1: THE DENDRITIC MOLECULAR STRUCTURE

Dendrimers possess three distinguished architectural components [5, 6], namely;

(i) A central core which is either a single atom or an atomic group having at least two identical chemical functions,
(ii) Branches emanating from the core, constituted of repeat units having at least one branch junction, whose repetition is organized in a geometrical progression that results in a series of radially concentric layers called generations, and
(iii) Many terminal functional groups, generally located in the exterior of the macromolecule, which play a key role in the properties.

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.

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'. 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.

Types of Dendrimers [5, 7]:

1. **Pamam Dendrimers:** PAMAM dendrimers represent an exciting new class of macromolecular architecture called "dense star" polymers. Poly(amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. PAMAM dendrimers are commercially available, usually as methanol solutions. ***Starburst dendrimers*** is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

2. **Pamamos Dendrimers:** Radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

3. **PPI Dendrimers:** PPI stands for "Poly (Propylene Imine)". These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consist of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology.

4. **Tecto Dendrimers:** These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

5. **Chiral Dendrimers:** The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core.

6. **Amphiphilic Dendrimers:** They are built with two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

7. **Micellar Dendrimers:** These are unimolecular micelles of water soluble hyper branched polyphenylenes.

8. **Multiple Antigen Peptide Dendrimers:** It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, *e.g.* vaccine and diagnostic research.

9. **Fréchet-Type Dendrimers:** It is a more recent type of dendrimer developed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalization, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media [8, 9].

Synthesis: Most syntheses of dendrimers involve the repetitious alternation of a growth reaction and an activation reaction. Many dendrimer syntheses rely upon traditional reactions, such as the Michael reaction [1, 2] or the Williamson ether synthesis [10], whilst others involve the use of modern techniques and chemistry, such as solid-phase synthesis [11], organotransition-metal chemistry [1], organosilicon [12] chemistry, organo-phosphorus chemistry [13], or other contemporary organic methodologies [14]. Dendrimers are generally prepared using either a divergent method or a convergent one.

1. **Divergent method:** The divergent approach (**Fig. 2**) was first introduced by Tomalia [15] and Newkome *et al*., [4] in the early-1980s. In this method, dendrimer grows outwards from the focal core, using a pair of basic operations that consist of:

   a. Coupling of building blocks, and;

   b. Deprotection or modification of end-functionalities of the periphery to create new reactive surface functionalities; this pair of basic operations is often referred to as the 'growth of a generation'.

The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. This process is repeated until the desired number of generations is obtained. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is doubled.

Very large dendrimers have been prepared in this way, but Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. It causes some difficulties in the purification of the final product.

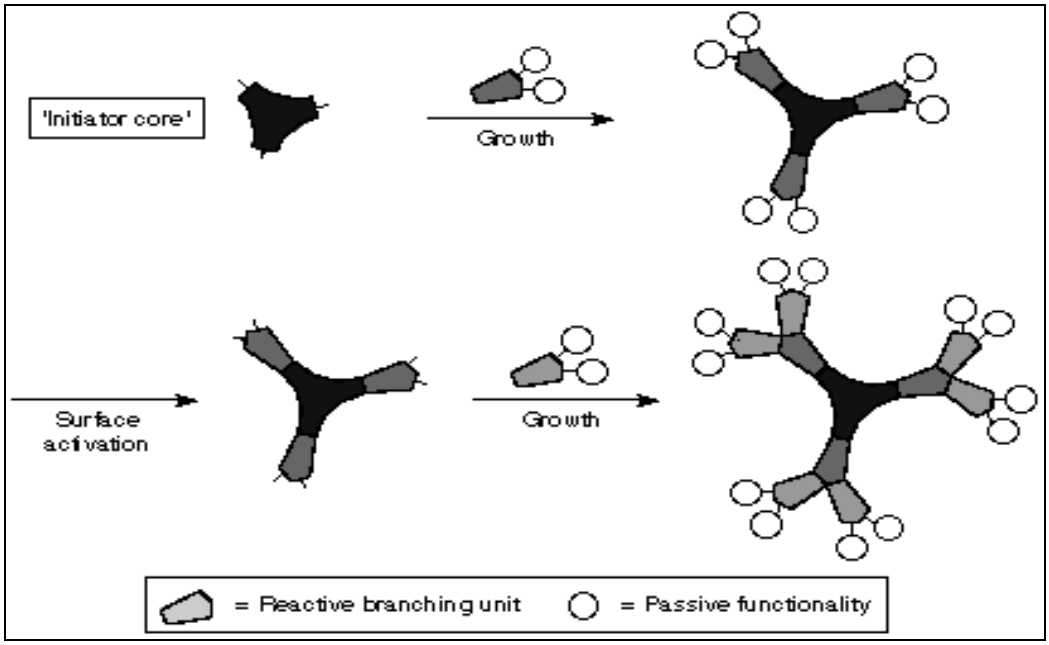

FIG. 2: DIVERGENT SYNTHESIS

2. **Convergent method:** The convergent growth strategy, pioneered by Hawker and Fréchet [16] emerged as an alternative method to the divergent approach for producing precisely controlled dendritic architectures. The convergent approach overcomes some of the problems associated with the divergent method. In the convergent approach, the dendrimer is constructed stepwise.

   Starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule (**Fig. 3**). The difference in mass between byproducts and the desired product is quite large, thus making purification of the desired products relatively simple. Occurrence of defects in final product is minimized because of the small number of simultaneous reactions carried out in each step. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule.

   Reactions under a convergent approach need a relatively longer time compared to that of the divergent method. In addition to the divergent and convergent approaches, various alternative preparation methods have been developed that aim to reduce the number of synthetic and purification steps and increase yields, such as the double-stage convergent growth approach [17], double-exponential dendrimer growth approach [18] and orthogonal coupling [19].

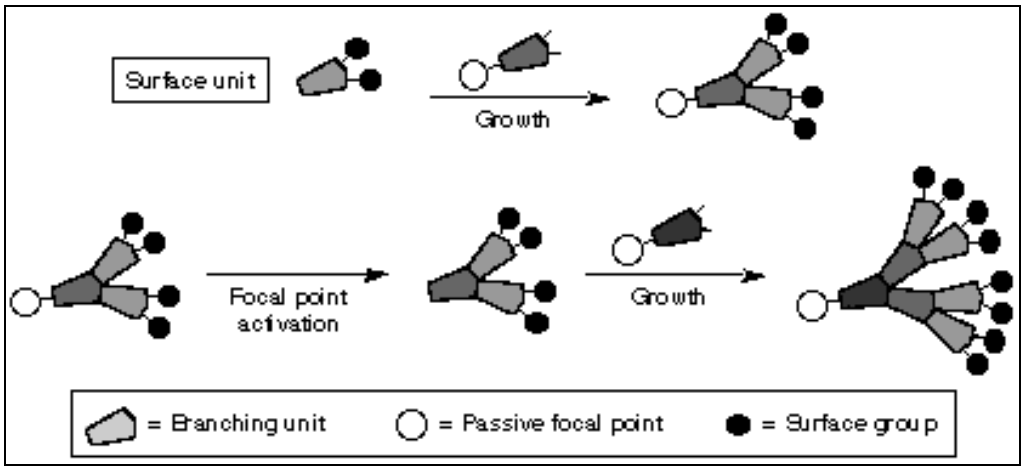

FIG. 3: CONVERGENT SYNTHESIS

Properties:

1. **Physicochemical properties:** Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers.

   a. Dendrimers are monodisperse macro-molecules; they generally have a uniform molecular weight and no specific molecular weight distribution.

   b. The size of the dendrimers increases systematically, as does the generation number, ranging from several to tens of nanometers in diameter. Unlike linear polymers, entanglement or interpenetration of dendrimers is generally unfavorable due to their densely packed surface.

   c. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solutions have a significantly lower viscosity than linear polymers [20].

The most exciting physical property of dendrimers is the variation of their intrinsic viscosities with molecular weight. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at fourth generation and then begins to decline (**Fig. 4**) [21]. This effect is believed to be a consequence of the globular shapes of high generation dendrimers leaving them unable to 'tangle' with one another after the manner of linear polymers.

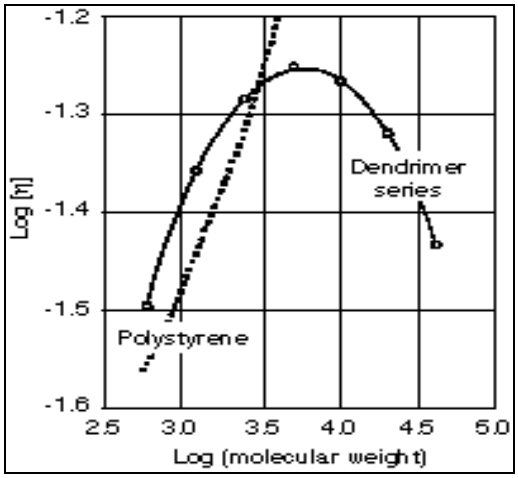

FIG. 4: INTRINSIC VISCOSITY BEHAVIOUR OF POLYETHER DENDRIMERS AND OF POLYSTYRENE

   a. The solubility of dendrimers is predominantly controlled by their peripheral functionalities. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers hydrophobic end groups are soluble in nonpolar solvents.

   b. In large dendrimers (i.e. generation > 4), the surface is highly congested, whereas a substantial amount of free space is encapsulated in the interior part, which allows for a wide range of applications such as site specific pockets for the accommodation of a variety of guest molecules.

Meijer and co-workers [22] trapped small molecules like rose bengal or p-nitrobenzoic acid inside the 'dendritic box' of poly(propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting the terminal amines with an amino acid (L phenylalanine) and guest molecules were stably encapsulated inside the box (**Fig. 5**). Hydrolyzing the outer shell could liberate the guest molecules.

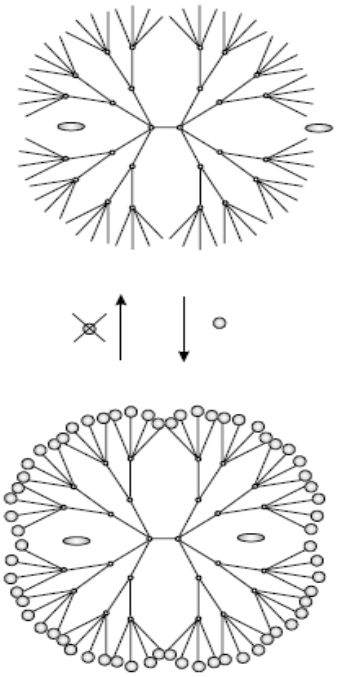

FIG. 5: DENDRITIC BOX ENCAPSULATING GUEST MOLECULES

2. **Biological properties:** In order to apply dendrimers to biomedical applications, they should satisfy at a minimum several levels of biological safety requirements involving less toxicity, biocompatibility, and immunogenicity testing.

When dendrimers are used as drug or gene carrier molecules, they should also have an appropriate biodistribution and permeability level combined with a tolerance to enzymatic attack in the blood stream. As mentioned previously, large dendrimers have a densely packed surface structure and a relatively free interior space that can be isolated from the external environment. Therefore, short-term cytotoxicity of sufficiently large dendrimers is predominantly determined by the nature of their surface functionalities.

"Cationic" dendrimers (e.g., amine terminated PAMAM and poly(propylene imine) dendrimers that form cationic groups at low pH) are generally hemolytic and cytotoxic. Dendrimers possessing a cationic surface destabilize the cell membrane and instigate cell lysis when present at a high enough concentration due to the negatively charged nature of the cellular membrane.

For example, Roberts and coworkers used V79 cells, a Chinese hamster lung fibroblast line, and male Swiss-Webster mice to study *in-vitro* and *in-vivo* toxicity, immunogenicity, and biodistribution of 3, 5 and 7th generation PAMAM dendrimers [23]. They found that the toxicity of the PAMAM dendrimers was both dose- and generation-dependent in vitro, whereas low generations (below 5th) were not toxic. PAMAM dendrimers (generation 2, 3 and 4) interact with erythrocyte membrane proteins causing changes in protein conformation. These changes increase with generation number and the concentration of dendrimers.

In fact, lower generation PAMAM dendrimers possessing carboxylate surface groups have neither haematotoxic nor cytotoxic activity over a broad range of concentrations[24]; however, dendrimers containing aromatic polyether building blocks and anionic carboxylate surface groups have been shown to have hemolytic activity against rat blood cells. In the case of PAMAM dendrimers with an anionic surface, significantly lower cytotoxicity of Caco-2 cells has been observed compared to cationic dendrimers.

Incubation of human red blood cells in plasma or suspended in phosphate-buffered saline with anionic PAMAM dendrimers causes the formation of cell aggregates. No changes in aggregability of nucleated cells such as Chinese hamster fibroblasts are observed. The surface functionality of dendrimers can be modified such that they are water-soluble and neutral. Such molecules, including hydroxy- or methoxy-terminated dendrimers, which are based on polyester dendrimers, have been explored as biomedical scaffolds.

Conjugation of poly(ethylene glycol) (PEG) to the surface of PAMAM dendrimers distinctly reduces the cytotoxicity towards Caco-2 cells. This observation can be explained via the reduction of overall positive charge of surface-modified dendrimers. PEG immobilization onto a dendrimer surface can also reduce immunogenicity and antigenicity by shielding the system from being recognized by the immune system. PEG chains increase the hydrophilicity of dendrimers, creating a highly hydrated dendrimer surface with a low disturbing effect on the physiological environment. Therefore, PEG modified dendrimers show reduced sequestration or uptake by a reticuloendothelial system and a prolonged circulation time in the body [25].

Applications: Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications. Some of the commercialised dendrimers are given in **table 1**.

TABLE 1: COMMERCIALISED DENDRIMERS

S. No.	PRODUCT	PURPOSE	COMPANY
1	VivaGel™	Prevention of HIV	StarPharma
2	Stratus® CS	Cardiac diagnostic testing	Dade Behring
3	SuperFect®	Gene transfection	Qiagen
4	Alert Ticket™	Anthrax detection	U.S. Army Research Laboratory

1. **Biomimetic applications of Dendrimers:** The unique monodisperse property of dendrimers, which is often compared with that of globular type natural proteins, endows dendrimers with the ability to mimic natural materials by exhibiting unexpectedly versatile characteristics such as self-assembly, site selective catalysis, and light harvesting.

a. **Self-assembly of Dendrimers:** Self-assembly is a fundamental phenomenon in natural systems necessary for constructing biologically active complexes, ranging from molecular-level organized structures to functional organelles. Dendrimers are promising building blocks for the construction of supramolecular functional materials due to their predictable and controllable three-dimensional structure. Also, due to the morphological similarity between dendrimers and biomolecules, the self-assembly of dendrimers provides a powerful model with which to understand biological assembling systems.

Self-assembly based on non-covalent interactions such as hydrogen-bonding, acid-base, electrostatic, metal-ligand, and van der Waals interactions have been extensively studied as an alternative to the covalent approach for fabrication of dendrimers. In non-polar solvents, the dendrimers form oligomeric aggregates because the saccharide moieties provide a driving force for aggregate formation due to hydrogen-bonding interactions. These temporary aggregates were subsequently converted into permanent architectures via cross-linking, thereby immobilizing the dendrons into permanent dendrimers [26]. The cholesterol modified dendrimer spontaneously assembled in water to form a micelle-like structure that was used to provide a new drug formulation by hydrotropic solubilization of paclitaxel.

b. **Dendrimers as a Site Selective Catalyst:** Catalysis is one of the most promising applications in dendrimer chemistry. There are two major strategies for constructing dendritic catalysts, with the first being introduction of multiple catalytic sites to the periphery of the dendrimers, resulting in enhanced catalytic activities and reaction rates compared to those of their parent monomeric catalytic compounds. The second strategy is the introduction of a catalytic site at the focal core, possibly resulting in a site selective nano-reactor due to the presence of interior void spaces that are isolated from the external environment. Several attempts have been made to use dendrimers to achieve regioselective catalysis.

For example, Suslick and co-workers reported that a series of manganese porphyrin-cored polyester dendrimers exhibit shape-selective catalytic epoxidation of olefins using iodosobenzene as an oxidant [27]. Compared to non-dendritic Mn(TPP)Cl, dendritic manganese porphyrins preferentially choose less sterically hindered double bonds to undergo epoxidation.

c. **Dendrimers for Artificial Light Harvesting:** A variety of dendrimer have been carefully designed and studied due to the fact that a large number of light-harvesting chromophores can be placed in the periphery and/or the branch units of dendrimer. Absorbing dyes are placed at the periphery of the dendrimer and transfer the energy of light to another chromophore located in the core. The absorption spectrum of the whole macromolecule is particularly broad because the peripheral chromophores cover a wide wavelength range. The energy transfer process converts this broad absorption into the narrow emission of the central dye. The light harvesting ability increases with generation due to the increase in the number of peripheral chromophores.

2. **Dendrimers for Drug Delivery:** Site-specific drug delivery and controlled release may significantly improve the effectiveness of drugs by reducing undesired localization, allowing for easier optimization of the drug concentration. Among the polymeric materials, dendrimers have attracted the most attention as potential drug delivery scaffolds due to their unique characteristics. Specifically, dendrimers can be used to deliver drugs either by encapsulating the drug in the dendrimer interior void spaces or by conjugation to surface functionalities [28].

a. **Dendrimers as Host Molecules:** One of the remarkable features of dendrimers is their unique density distribution, e.g., the relatively flexible inner space around the focal core and the densely packed peripheral functionalities. This structural property has a potential for use as a host molecule for encapsulating small molecules into the flexible inner space. Alternatively, the highly functional surface of dendrimers can be used for multiple binding interactions.

In pioneering work, Meijer and co-workers reported the creation of a dendritic box [22], which has protected amino acid groups on the 64 amine terminal of the PPI dendrimers. This dendrimer could simultaneously bind up to 4 large guest molecules (Rose Bengal) and 8–10 small guest molecules (p-nitrobenzoic acid). Upon deprotection of the terminal functionalities, the surface shell opened and the guest molecules were allowed to leak from the dendrimer (Fig. 5).

b. **Drug Delivery:** Various therapeutic agents have been examined as guest molecules for drug delivery. Ibuprofen, an anti-inflammatory drug, was evaluated by complexation and encapsulation into 3rd and 4th generation PAMAM dendrimers. In this study, up to 78 ibuprofen molecules were found to be complexed by the PAMAM dendrimers through electrostatic interactions between the amine groups of the dendrimer and the carboxyl group of the drug, and the in vitro release of ibuprofen from the complex was appreciably slower compared to free ibuprofen. The complexed drug delivery structure was found to enter A549 cells much more rapidly than the free drug, suggesting that dendrimers may be able to efficiently carry complexed drugs inside of cells [29].

Villiers and coworkers [30] have researched the effect of PAMAM dendrimer size on the solubility of the hydrophobic drug nifedipine, a calcium channel-blocking agent, within an aqueous medium. They found that the increase in drug solubility in aqueous PAMAM dendrimer solutions depended on the size of the dendrimer, where the drug solubility increased with the size of the dendrimers. The PAMAM dendrimers were shown to be effective at increasing the flux of indomethacin in transdermal delivery *in vitro* as well as *in vivo* due to the increase in solubility of indomethacin by the dendrimers [31]. The anticancer drug cisplatin conjugated with PAMAM has a slower release profile and higher accumulation in solid tumors, along with lower toxicity, compared to unconjugated cisplatin [32].

c. **Gene Delivery:** Various polycationic compounds such as PEI, polylysine, and cationic liposome have been utilized as non-viral gene carriers. **Fig. 6** shows a plausible mechanism of gene transfection with non-viral vectors, where the formation of a complex between negatively charged DNA and polycationic compounds is the initial step for such non-viral gene transfection. The complexed DNA with polycations associates with the cellular membrane and internalizes into the intracellular compartment through an endocytotic pathway. For effective gene expression, the DNA should be able to efficiently escape from the endosomal compartment to the cytosol and then be transferred to the nucleus. Commercially available PAMAM and PPI dendrimers are the most representative dendrimers for use as non-viral gene carriers because of their relatively low cytotoxicity and high affinity to negatively charged genes. [33, 34, 35], similar to other polycationic compounds, PAMAM or PPI.

Dendrimers form complexes with DNA through electrostatic interactions between the negatively charged phosphate groups of nucleic acids and the protonated primary amino groups on the dendrimer surface. In addition to the primary amino groups on the dendrimers surface, PAMAM or PPI dendrimers have tertiary amino groups in the branching points. Tertiary amino groups have a high buffering capacity, which enables dendrimers to act as a weak base and retard degradation caused by acidification within the endosome–lysosome. A change in the ion-osmotic pressure might also lead to swelling of the complexes within the endosome, which can possibly disrupt the endosomal membrane and promote the release of the DNA complex.

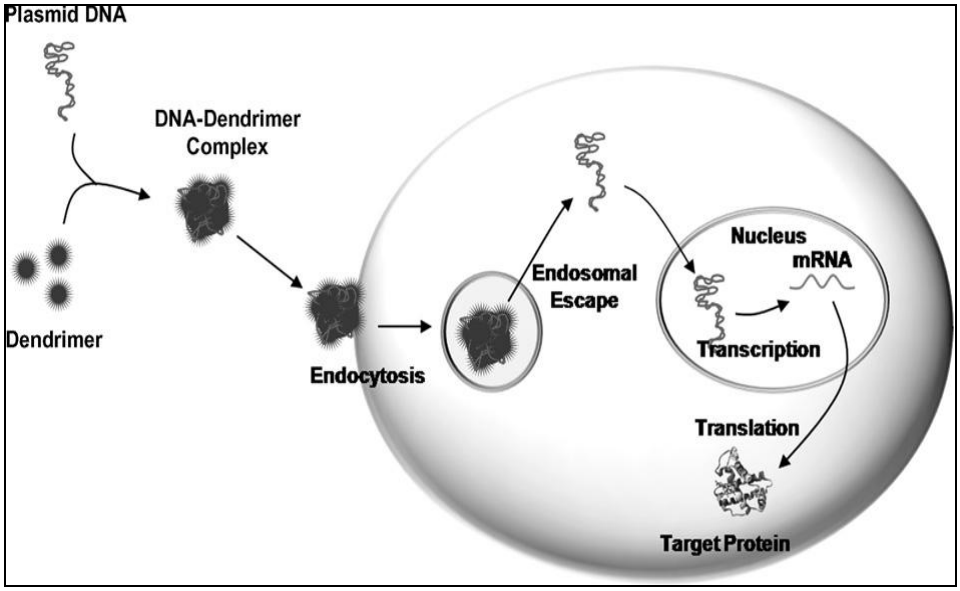

FIG. 6: MECHANISM OF GENE TRANSFECTION WITH DENDRITIC GENE CARRIER

3. **Therapeutic applications of Dendrimers:**

a. **Dendrimers for Chemotherapy:** The multivalency of a dendrimer's surface is very useful for immobilizing a large number of functional materials. Immobilization of biocides on a dendritic surface can be utilized to design novel effective antimicrobial [36, 37]. In this example, Cooper and co-worker prepared a PPI dendrimer with 16 quaternary ammonium compounds (QACs) having long alkyl chain substitutions that have been widely used as disinfectants.

Although the exact mechanism of the antimicrobial activity of QACs is not yet fully understood, it is currently thought to be due to their ability to increase cell permeability and cell membrane disruption. QAC-immobilized PPI dendrimers have been shown to have very high antibacterial activity against both Gram-positive and Gram-negative bacteria compared to QACs-immobilized hyperbranched polymers [38].

The route of virus internalization in a cell generally depends on the recognition of specific receptors on the cell surface and fusion with the cellular membrane. In certain cases viruses recognize acidic carbohydrates of the mammalian cell surface. Therefore, a kind of polyanionic-surfaced dendrimer could possibly inhibit the internalization of viruses by means of competition with the negatively charged cell surface. For example, PAMAM dendrimers with phenyldicarboxylic acid or naphthyl sulfonate residues at the surface have been observed to have antiviral activity. In addition, poly (l-lysine) dendrimers with naphthyl residues and sulfonate surface groups were found to be useful as viral inhibitors for the Herpes Simplex virus *in vitro* [39]. Another well-known therapeutic application of dendrimers is the use of multiple antigen peptides (MAPs). [40] For the preparation of well-defined, reproducible immunogens, a high molecular weight carrier is necessary.

In this respect, dendrimers have a high potential for use as a scaffold for immunogen carriers because dendrimers can be easily modified by coupling antigen molecules to the surface functional groups. The first example of MAPs was reported by Tam and co-worker, who synthesized defined mixtures of B- and T-cell epitopes by attaching multiple copies of the peptide sequences to the polylysine dendrimer core.

Compared to traditional methods, the small peptide dendrimer can act as a very strong immunogen. Indeed, a MAP-based malaria vaccine is already in phase I human clinical trials. [40]

CONCLUSION: In this review, we have summarized historical and all recent developments in the field of dendrimers. And we discussed very elobarately about characterization techniques and applications of dendrimers.

Inspite of potential applications of dendrimers, they have their own disadvantages like unpredictable dendrimer toxicity and biodistribution on which no extensive research has taken place till now. Finally, authors would like to say that some more research has to take place on effects of dendrimer core, terminal group chemistry, size, shape, hydrophobicity on dendrimer interactions with cell membranes, fate of dendrimers and tranport of dendrimers in the environment to remove the ambiguity about the safety of dendrimers and to make them an excellent substitute for polymers in the future.

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