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DENDRIMER: A COMPLETE DRUG CARRIER

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ABSTRACT

Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. Structural Advantages allow dendrimers to play an important role in the fields of nanotechnology, pharmaceutical and medicinal chemistry. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications. The paper gives a brief review of dendrimers' physico-chemical properties and their possible use in various areas of research, technology and treatment.

INTRODUCTION: A dendrimer is generally described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers have often been refered to as the "Polymers of the 21st century". Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers [1]. He synthesized the first "cascade molecules". In 1985, Donald A. Tomalia, synthesized the first family of dendrimers [2]. The word "dendrimer" originated from two words, the Greek word *dendron*, meaning tree, and *meros*, meaning part. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.

Ideally dendrimers are perfect mono-dispersed macromolecules with regular and highly branched three-dimensional architecture. "Dendron" means tree like in Greek (synonymous with "arborol" in Latin) and "meros" meaning part. They are nanoscopic in size about 1 to 100 nm [3]. Dendrimers differ from classical random coil molecules in that they consist of three distinguishing architectural components: an interior core, interior layers (generations) composed of repeating units readily attached to the interior core and exterior (terminal functionality) attached to the interior generation [4]. Major difference between linear polymers and dendrimers is that a linear polymer consists of long chains of molecules like coils whereas dendrimers consist of molecular chains that branch out from a common centre and there is no entanglement between dendrimer molecules.

Structure of Dendrimer: Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex. Dendrimers possess three distinguished architectural components [5], namely;

- An initiator core.
- Interior layers (generations) composed of repeating units, radically attached to the interior core.
- Exterior (terminal functionality) attached to the outermost interior generations

Components of a Dendrimer Structure:

Generation: It is the hyper branching when going from the centre of the dendrimer towards the periphery, resulting in homo-structural layers between the focal points (branching points). The number of focal points when going from the core towards the dendrimer surface is the generation number. That is a dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer. Here, we

abbreviate this term to simply a G5-dendrimer.The core part of the dendrimer is sometimes denoted generation “zero”, or in the terminology presented here “G0”.

Shell: The dendrimer shell is the homo-structural spatial segment between the focal points, the “generation space”. The “outer shell” is the space between the last outer branching point and the surface. The “inner shells” are generally referred to as the dendrimer interior.

Pincer: In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface. In PPI and PAMAM dendrimers the number of pincers is half the number of surface groups (because in these dendrimers the chain divides into two chains in each focal point).

End-group: It is also generally referred to as the “terminal group” or the “surface group” of the dendrimer. Dendrimers having amine end-groups are termed “amino-terminated dendrimers”[6] (Fig. 1).

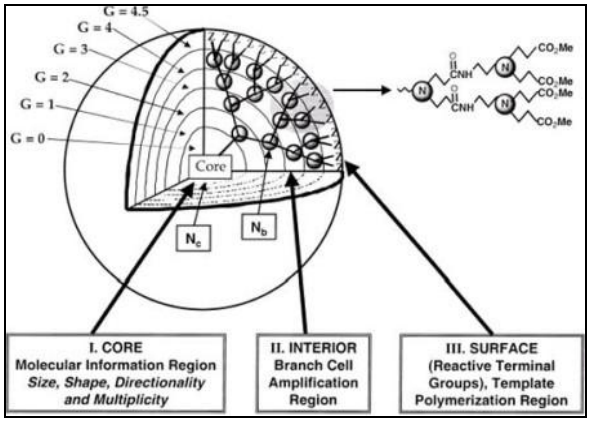

Fig. 1: Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface

Dendrimer Synthesis: Three fundamentally different methods have been developed for stepwise synthesis of dendritic polymers.

Divergent growth method: This type of synthesis involves addition of branching monomer units repeatedly on to produce a dendrimer desired generation number. Starting from a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers. The two steps can be repeated. 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 (Fig. 2).

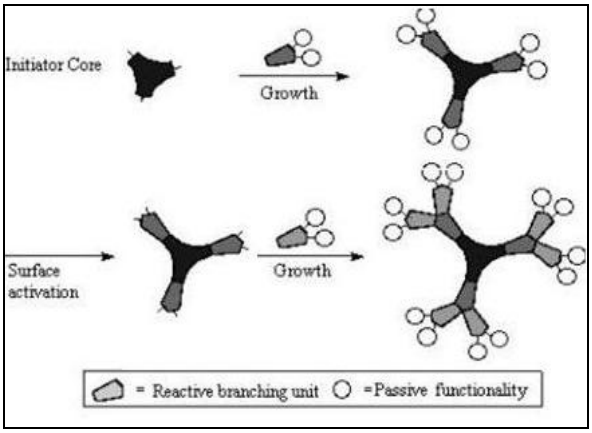

Fig. 2: Divergent growth method

Convergent growth method: The 'convergent' approach was developed as a response to the weaknesses of divergent syntheses. Convergent 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. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step [7] (Fig. 3).

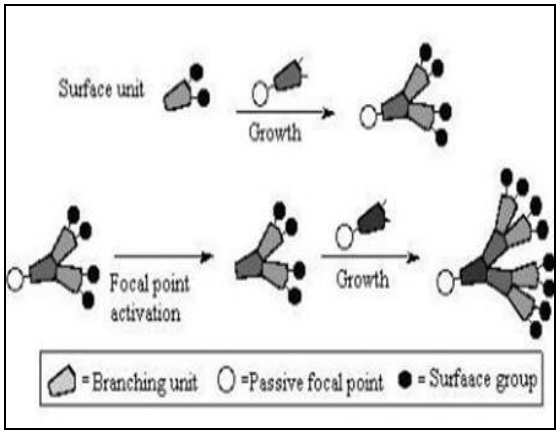

Fig. 3: Convergent growth method

Double Exponential' and 'Mixed' Growth: The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB2 monomer with orthogonal protecting groups for the A and B functionalities. This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material[8].

These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. The double exponential methodology provides a means whereby a dendritic fragment can be extended in either the convergent or the divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings [7] (Fig. 4).

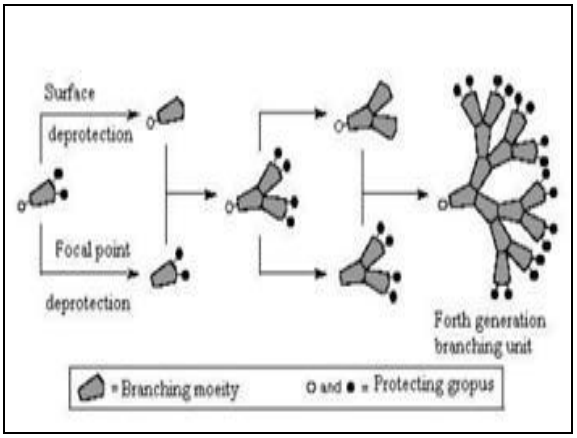

Fig. 4: Double Exponential and Mixed Growth

Types of Dendrimers:

Pamam Dendrimer: Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10 [9] (a molecular weight of over 9, 30,000 g/mol) have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). 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 starlike pattern observed

when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

Pamamos Dendrimer: 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.

PPI Dendrimer: PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vögtle [10]. These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists 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. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine), which closely resembles the PPI abbreviation. In addition, these dendrimers are also sometimes denoted "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

Tecto Dendrimer: 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.

Multilingual Dendrimers: In these dendrimers, the surface contains multiple copies of a particular functional group.

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

Hybrid Dendrimers Linear Polymers: These are hybrids (block or graft polymers) of dendritic and linear polymers.

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

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

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.

Frechet-Type Dendrimers: It is a more recent type of dendrimer developed by Hawker and Fréchet [11] 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 functionalisation, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media.

Advantages of Dendrimers: Dendrimers offers various advantages over other polymers: [12]

- Dendrimers have nanoscopic particle size range from 1 to 100 nm, which makes them less susceptible for RES uptake.
- Due to stringent control during synthesis, they have lower polydispersity index. As the density of branches increases the outer most branches arrange themselves in the form of spheres surrounding a lower density core and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.
- Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body.
- Dendrimers can be modified as stimuli responsive to release drug.
- Dendrimers might show an enhanced permeability and retention effect (depending on their molecular weight) that allows them to target tumor cells more effectively than small molecules.

Mechanisms of Drug Delivery: Dendrimers are particularly attractive as they offer a high drug-loading capacity. Two methods of dendrimer drug delivery are encapsulation of drugs and dendrimer – drug conjugates.

Noncovalent Encapsulation of Drugs / Host – Guest Relation: Encapsulation of drugs uses the satiric bulk of the exterior of the dendrimer or Interactions between the dendrimer and drug to trap the drug inside the dendrimer Maciejewski introduced the concept of encapsulating guest molecules into special, egg-shell-like structures. Such a system can be used to encapsulate drugs and provide controlled delivery. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications, and hydrophobic drugs and dye molecules were incorporated into various dendrimer cores. An advantage of using dendritic unimolecular micelles rather than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected.

Although the introduction of stabilizing PEO chains on the dendrimer periphery has expanded the scope of dendritic unimolecular micelles to incorporate anticancer drugs such as 5-fluorouracil methotrexate and doxorubicin and can slow the drug release rates in these systems to some extent. A promising new approach to controlling the release of drugs from the encapsulating micellar compartment involves the use of hybrids of PEO and dendrimers with pH-sensitive

hydrophobic acetyl groups on the dendrimer periphery [13].

Covalent Dendrimer–Drug Conjugates: An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multi valency for the covalent attachment of drug molecules to the dendrimer periphery. In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids .The drug loading can be tuned by varying the generation number of the dendrimer, and release of the drug can be controlled by incorporating degradable linkages between the drug and dendrimer. Conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with non-specific toxicity and poor water solubility.The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors. [14].

Surface modification of dendrimers: In order to increase water solubility, biocompatibility and to reduce toxicity, it is necessary to change the surface of the dendrimers. Now a day, considerable effort has been dedicated to the preparation of dendrimers that are designed to be highly biocompatible and water soluble. In addition, some dendrimers have been designed to be biodegradable, e.g., polylysine [15]. Dendrimers having carbohydrate moiety at core or periphery have been widely explored and are emerging as promising immunological tools because of their multivalent binding capacity [16,17] prepared different polyester dendrimers incorporating monomers such as glycerol, succinic acid, phenylalanine, etc. Bhadra *et al* [18] synthesized PEGylated dendritic nano carrier for the delivery of fluorouracil. The PEGylated dendrimer has shown to increase drug loading but reduced drug release and hemolytic toxicity of dendrimers [19] Majoros studied the nature of the acetylation reaction and reported a method for the preparation of an acylated macromolecule, which can serve as a scaffold for complex dendrimeric structures. Acetylated G5 PAMAM dendrimer represents a more compact structure than the nonacetylated G5 PAMAM dendrimer. In Ref [20] the enhancement of gene transfer activity mediated by mannosylated dendrimer/alpha cyclodextrin activity conjugate has been studied. Jevprasesphant *et al*. prepared lauryl-dendrimer conjugates to enhance transepithelial transport and reduce cytotoxicity [21].

Properties of Dendrimers: Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional

linear polymers. 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 significantly lower viscosity than linear polymers [22]. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline [23]. Such behavior is unlike that of linear polymers. For classical polymers the intrinsic viscosity increases continuously with molecular mass.

The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity [22]. 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. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester. A marked difference was also observed in chemical reactivity. Dendritic polyester was debenzylated by catalytic hydrogenolysis whereas linear polyester was unreactive.

Lower generation dendrimers which are large enough to be spherical but do not form a tightly packed surface, have enormous surface areas in relation to volume (up to 1000 m^2/g) [24]. Dendrimers have some unique properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior. Meijer and co-workers [25, 26] 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).

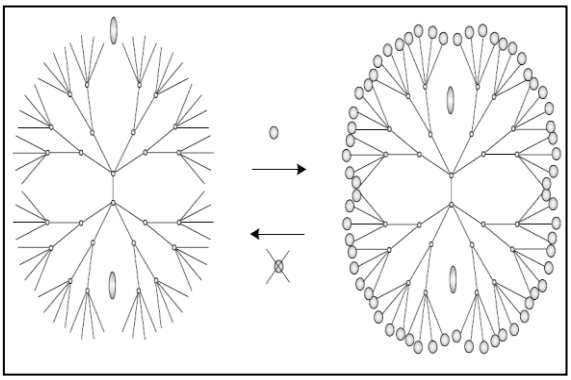

Fig.5: 'Dendritic box' encapsulating guest molecules

Hydrolysing the outer shell could liberate the guest molecules. The shape of the guest and the architecture of the box and its cavities determine the number of guest molecules that can be entrapped. Meijer's group described experiments in which they had trapped four molecules of rose bengal or eight to ten molecules of *p*-nitrobenzoic acid in one dendrimer. Archut and co-workers [27] developed a method in which boxes could be opened photochemically. A fourth generation polypropylene imine dendrimer with 32 end groups was terminated in azobenzene groups (Fig. 6).

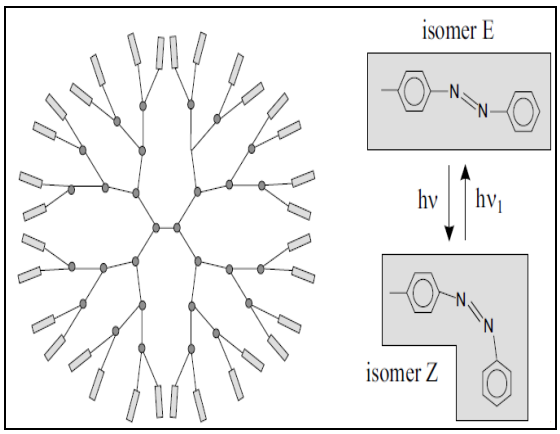

Fig.6: Dendrimer terminated in Azobenzene groups

The azobenzene groups undergo a fully reversible photoisomerization reaction. The E isomer is switched to the Z form by 313 nm light and can be converted back to the E form by irradiation with 254 nm light or by heating. Such dendrimers can play the role of photoswitchable hosts for eosin Y. Photochemical modifications of the dendritic surface cause encapsulation and release of guest molecules. Archut's experiment demonstrated that the Z forms of the fourth generation dendrimers are better hosts than the E forms. It is possible to create dendrimers which can act as extremely efficient light-harvesting antennae [28, 29]. 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.

Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications. "Cationic" dendrimers (e.g., amine terminated PAMAM and poly (propylene imine) dendrimers that form cationic groups at low pH) are generally haemolytic and cytotoxic. Their toxicity is generation-dependent and increases with the number of surface groups [30].

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. The interactions between proteins and half-generation PAMAM dendrimers (2.5 and 3.5) are weaker 1. Anionic dendrimers, bearing a carboxylate surface, are not cytotoxic over a broad concentration range [31]. Incubation of human red blood cells in plasma or suspended in phosphate-buffered saline with PAMAM dendrimers causes the formation of cell aggregates. No changes in agreeability of nucleated cells such as Chinese hamster fibroblasts are observed [32].

Applications of Dendrimers:

There are following precise reasons which make the dendrimer an effective carrier for the drug delivery system.

- Can be precisely designed and manufactured, permits tunable

solubility, low toxicity and bio-attachment capability.

- Forms uniform shell structure
- Possibilities of adjusting physical and chemical properties by altering chemistry

Dendrimer in drug delivery:

Dendrimer drug conjugates: Drug molecules can be either chemically conjugated to the dendrimer surface or physically encased inside a dendrimer core. For chemical conjugations, a good coupling efficiency may be achieved if functional groups are activated prior to coupling. Hydroxyl (OH), carboxyl (COOH), primary amine (NH_2), thiol (SH) and guanidino are commonly found functional groups in drug molecules and polymers. Hydroxyl groups can be converted to active intermediates that favor nucleophilic reactions. For example, coupling hydroxyl groups with primary amine groups causes primary amine groups to form secondary amines or stable carbamate bonds. Amides are relatively stable in basic, acidic and enzymatic conditions.[33.] PAMAM dendrimers form conjugates with 5FU, which are water soluble and releases free 5FU slowly on hydrolysis of the conjugate, thereby reducing the toxicity[34].

Dendrimers can be used as coating agents to protect or deliver drugs to specific sites in the body or as time-release vehicles for biologically active agents. Well defined and macromolecular structure of dendrimer offers the polyvalent characteristic. Through polyvalent interactions with receptors and binding sites, dendrimers may be designed to achieve higher activity than small molecules. In addition, dendrimers may be constructed and modified to have longer duration of action, reduced side effects and other beneficial effects compared with currently available pharmaceuticals. Branched poly (l-glutamic acid) chains were centered on PAMAM dendrimers to create new biodegradable polymers with improved biodistribution and targeting ability. These constructs were surface-terminated with poly (ethylene glycol) chains to enhance their biocompatibility and folic acid receptors to introduce cell-specific targeting[35].

Solubility enhancer: PAMAM dendrimers possess empty internal cavities that can encapsulate hydrophobic guest molecules in the macromolecule interior. Drugs or other molecules can either be attached to dendrimers' end groups or encapsulated in the macromolecule interior. These specific properties make dendrimers suitable for drug delivery systems. Dendrimers can be used as the carriers to increase the solubility of drug [36]. The effect of PAMAM dendrimer generation, its size and surface functional groups on the aqueous solubility, and therefore, the bioavailability of nifedipine have been studied [37]. The solubility enhancement of nifedipine was higher in the presence of ester-terminated dendrimers than their amino-terminated analogues possessing the same number of surface groups.

Transdermal drug delivery: PAMAM dendrimers enhanced the bioavailability

of indomethacin in transdermal delivery applications.[38] Wang *et al* [39] reported the utilization of polyhydroxyalkanoate and G 3 PAMAM dendrimers as Transdermal drug delivery (TDDS). Cheng *et al*. [40] investigated TDDS for anti-inflammatory drugs and concluded that the bioavailability of anti-inflammatory drugs was increased; it may be due to the facilitated skin penetration.

Ocular drug delivery: Vandamme and Broberck [41] have reported the development of ophthalmic vehicles in ocular drug delivery using PAMAM dendrimers for pilocarpine nitrate. They found that there is more ocular residence time and significantly increased bioavailability by using PAMAM dendrimers.

Dendrimers in Gene Transfection: Dendrimers can act as vectors, in gene therapy. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus [42]. A transfection reagent called SuperFectTM consisting of activated dendrimers is commercially available. Activated dendrimers can carry a larger amount of genetic material than viruses. SuperFect–DNA complexes are characterized by high stability and provide more efficient transport of DNA into the nucleus than liposomes. The high transfection efficiency of dendrimers may not only be due to their well-defined shape but may also be caused by the low pK of the amines (3.9 and 6.9). The low p*K* permit the dendrimer to buffer the pH change in the endosomal Compartment [43] (Fig. 7).

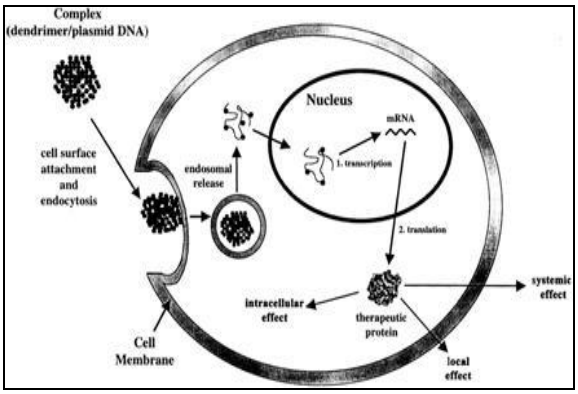

Fig. 7: Dendrimers in Gene Transfection

Dendrimers as Nano- Drugs: Poly (lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs)[42]. In earlier studies, it was found that PAMAM dendrimers covalently modified with naphthyl sulfonate residues on the surface also exhibited antiviral activity against HIV. This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities. PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be potent antibacterial biocides against Gram positive and Gram negative bacteria. Poly (lysine) dendrimers with mannosyl surface groups are effective inhibitors of the adhesion of E. coli to horse blood cells in a haemagglutination assay, making these structures promising

antibacterial agents. Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications

Nano-devices: The characteristic non toxicity of PAMAM dendrimers to biological systems makes their biocompatibility considerably greater than that of many other materials currently researched for use as controlled, chemotherapeutic drug delivery systems.[44]. The multifunctionality and biocompatibility of dendrimer-based nanodevices are crucial for the development of targeted drug delivery technology. Multifunctional cancer therapeutic nanodevices have been designed and synthesized using the PAMAM dendrimer as a carrier. Partial acetylation of amine-terminated PAMAM dendrimer can be used to neutralize a fraction of the primary amino groups, provide enhanced solubility of the dendrimer during the conjugation reaction of fluorescein isothiocyanate (FITC) in dimethyl sulfoxide (DMSO), and prevent nonspecific targeting interactions (*in vitro* and *in vivo*) during delivery.

Dendrimers as imaging agents: Macromolecular contrast agents have become very important tools of modern diagnostic medicine. An early application of dendrimer to imaging technology was disclosed in the US patent [45]. The patent discloses the new stable complexing agent for radionucleotide- derivatized phosphonate dendrimers imaging the skeletal system in mammals. Dendrimers provide multiple binding sites on the periphery, allowing many magnetic resonance imaging (MRI) contrasting agent complexes to attach to them. One dendrimer molecule can host up to 24 contrasting agent complexes (depending on generation), thereby attaining a higher signal to noise ratio. [46].

Dendritic Catalysts / Enzymes: The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. 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 [47]. Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Because of their 'pseudo'-spherical nature and their resultant conformations the metal sites in these well-defined polymeric catalysts should be easily accessible for substrate molecules and reagents, and therefore exhibit characteristics- fast kinetics, specificity and solubility [48].

CONCLUSION: The high level of control over the architecture of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds ideal carriers in biomedical application such as drug delivery, gene transfection and imaging. . Despite two decades since the discovery of dendrimers the multi-step synthesis still requires great effort. Unless there is a significant breakthrough in this field, only few applications for which the unique dendrimer structure is crucial will pass the

cost-benefit test. This review of dendrimer, a complete drug carrier, clearly illustrates the potential of this new "fourth architectural class of polymers" and substantiates the high optimism for the future of dendrimers in this important field.

REFERENCES:

1. Buhleier E, Wehner W and Vogtle F: Cascade and Nonskid-chain-like Synthesis of Molecular Cavity Topologies. Synthesis 1978; 2: 155-158.
2. Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J and Smith P: A New Class of Polymers: Starburst-Dendritic Macromolecules. Polymer Journal 1985; 17: 117-132.
3. Jain NK, Khopade AJ: Dendrimer as potential delivery system for bioactives' In: Jain NK. Edited "Advances in controlled and novel drug delivery. CBS publisher and distributors, New Delhi, Edition 1, 2000: 361-80.
4. Tomalia DA, Berry V, Hall M, and Headstrand DM: Macromolecules 1987; 20: 1164-9.
5. Pushkar S, Philip A, Pathak K and Pathak D: Dendrimers: Nanotechnology Derived Novel Polymers in Drug Delivery. Indian Journal of Pharmaceutical Education and Research 2006; 40:153-158.
6. Sakthivel T and Florence A.T: Adsorption of Amphipathic Dendrons on Polystyrene Nanoparticles. International Journal of Pharmaceutics 2003; 254:23-26.
7. Barbara K and Maria B: Review Dendrimers: properties and applications. Acta Biochimica Polonica2001; 48:199–208.
8. Sonke S and Tomalia DA: Dendrimers in biomedical applications reflections on the Field. Advanced Drug Delivery Reviews 2005; 57:2106 – 2129.
9. Hawker C and Fréchet JMJ: A new convergent approach to monodisperse dendritic molecule. Journal of the Chemical Society, Chemical Communications 1990;15: 1010-1012.
10. Hawker C, Wooley K.L and Fréchet J.M.J, J.Chem. Soc. Perkin. Trans ., 1, 1287-1289, 1993.
11. Yiyun C, Zhenhua X, Minglu M and Tonguen X: Dendrimers as Drug Carriers: Applications in Different Routes of Drug. Journal of Pharmaceutical Sciences 2008; 97: 123-143.
12. Maeda H, Fang J, Inutsuka T, Kitamoto Y. Vascular permeability enhancement in solid tumors: various factors, mechanisms involved and its implications. International Immunopharmacology. 2003; 3:319–328.
13. R. P. Patel et al. "Dendrimers: A new innovation in drug delivery", Pharma Bio World, 42-52, 2007.
14. Gillies ER and Fréchet JMJ: Dendrimers and dendritic polymers in drug delivery. Drug Discovery Today 2005; 10: 35-43.
15. Denkewalter RG: Macromolecular highly branched diaminocarboxylic acids. Chemical Abstracts 1984; 100:103907.
16. Bezouska K: Design, functional evaluation and biomedical applications of carbohydrate dendrimers (glycodendrimers). Journal of Biotechnology 2002; 90:269-90.
17. Grinstaff MW: Biodendrimers: New polymeric biomaterials for tissue engineering. Chemistry 2002; 8:2839-46.
18. Bhadra S, Bhadra D, and Jain NK: PEGylated Dendritic nanoparticulate carrier of fluorouracil. International Journal of Pharmaceutics 2003; 257:111-24.
19. Istvan JM, Scott W, and Baker JR: Acetylation of Poly (amidoamine) Dendrimers. Macromolecules 2003; 36:5526-9.
20. Uekama K, Chihara Y, and Koki W: Enhancement of gene transfer activity mediated by mannosylated dendrimer/alpha cyclodextrin activity conjugate. Journal of controlled release 2006; 116:64-74.
21. Jevprasesphant R, Penny F, Attwood D, and McKeown NB: Engineering of dendrimer surfaces to enhance transepithelial transport and reduce cytotoxicity. Pharmaceutical Research 2003; 20:1543-50.
22. Fréchet JMJ: Functional polymers and dendrimers: Reactivity, molecular architecture, and interfacial energy. Science 1994; 263: 1710–1715.
23. Mourey TH, Turner SR, Rubenstein M, Fréchet JMJ, Hawker CJ, and Wooley KL: Unique behaviour of

dendritic macromolecules: Intrinsic viscosity of polyetherdendrimers. Macromolecules 1992; 25: 2401–2406.

24. Alper J: Rising chemical "stars" could play many roles. Science 1991; 251: 1562–1564.

25. Jansen, JFGA, de Brabander van den Berg EMM & Meijer EW: Encapsulation of guest molecules into a dendritic box. Science 1994; 266: 1226–1229.

26. Jansen JFGA and Meijer EW: The dendritic box: Shape-selective liberation of encapsulated guests. Journal of the American Chemical Society 1995; 117: 4417–4418.

27. Archut A, Azzellini GC, Balzani V, Cola LD and Vogtle F: Toward photoswitchable dendritic hosts. Interaction between azobenzene-functionalized dendrimers and eosin. Journal of the American Chemical Society 1998; 120: 12187–12191.

28. Gilat SL, Adronov A. and Frechet JMJ: Light harvesting and energy transfer in novel convergently constructed dendrimers. Angewandte Chemie International Edition.1999; 38: 1422–1427.

29. Adronov, A, Gilat SL, Frechet JMJ, Ohta K, Neuwahl FVR and Fleming GR: Light harvesting and energy transfer in laser-dye-labelled poly (aryl ether) dendrimers. Journal of the American Chemical Society 2000; 122: 1175–1185.

30. Roberts JC, Bhalgat MK and Zera RT: Preliminary biological evaluation of polyaminoamine (PAMAM) Starburst dendrimers. Journal of Biomedical Materials Research 1996; 30: 53–65.

31. Malik N, Wiwattanapatapee R, Klopsch R, Lorenz K, Frey H, Weener JW, Meijer EW, Paulus W & Duncan R: Dendrimers: Relationship between structure and biocompatibility *in vitro*, and preliminary studies on the biodistribution of 125 I-labelled polyamidoamine dendrimers *in vivo*. Journal of Controlled Release 2000; 65: 133–148.

32. Domañski, DM, Faber MA, Bryszewska M and Leyko W: 1st International Dendrimer Symposium, Frankfurt/Main; Book of Abstracts ;1999: 63.

33. Yang H, and Kao WJ: Dendrimers for pharmaceutical and biomedical applications. Journal of Biomaterials Science, Polymer Edition 2006; 17:3-19.

34. Zhuo RX: *In vitro* release of 5-fluorouracil with cyclic core dendritic polymer. Journal of controlled release 1999; 57:249-57.

35. Tansey W, Cao XY, Pasuelo MJ, and Wallace S: Synthesis and characterization of branched poly (l-lutamic acid) as a biodegradable drug carrier. Journal of controlled release 2004; 94:39-51.

36. Milhem OM, Myles C, McKeown NB, and D'Emanuele A: Polyamidoamine Starburst dendrimers as solubility enhancers. International Journal of Pharmaceutics 2000; 197:239-41.

37. Devarakonda B, Hill RA, and Villiers MM: The effect of PAMAM dendrimer generation size and surface functional group on the aqueous solubility of nifedipine. International Journal of Pharmaceutics 2004; 284:133-40.

38. Chauhan AS, Jain AK, and Jain NK: Dendrimer-mediated transdermal delivery: Enhanced bioavailability of indomethacin. Journal of controlled release 2003; 90:335-43.

39. Wang ZX, Yoshiaki I, and Yoshifumi H: Mechanism of enhancement of effect of dendrimers on transdermal permeation through polyhydroxyalkanoate matrix. Journal of Bioscience and Bioengineering 2003; 96:537-40.

40. Cheng YY, Man N, and Xu TW: Transdermal delivery of nonsteroidal anti inflammatory drugs mediated by PAMAM dendrimers. Journal of Pharmaceutical Sciences 2006; 96:595-602.

41. Vandamme TF and Broberck L: PAMAM dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. Journal of controlled release 2005; 102:23-38.

42. Sonke S and Tomalia DA: Dendrimers in biomedical applications reflections on the Field. Advanced Drug Delivery Reviews 2005; 57: 2106 – 2129.

43. Barbara K and Maria B: *Review* Dendrimers: properties and applications. Acta Biochimica Polonica 2001; 48:199–208.

44. Istvan JM, Thommey PT, and Chandan B: Poly (amidoamine) dendrimer-based multifunctional engineered nanodevice for cancer therapy. Journal of Medicinal Chemistry 2005; 48: 5892-9.

45. Fahlvik, Simon. Ultrafine lightly coated superparamagnetic Particles for MRI. US patent 4606907.

46. Sheela DK, Michael A, and Steven W: Specific targeting of folate-dendrimer MRI contrast agents to

the high affinity folate receptor expressed in ovarian tumor xenografts. MAGMA 2001; 12: 104-13.

47. Kleij AW, Ford A, Jastrzebskl H and Vankoten G: Dendritic Polymer Applications: Catalysts", Edited by Fre´chet J.M.J and Tomalia D.A., 485-507.

48. Kofoed J and Reymond J: Dendrimers as artificial enzymes. Current Opinion in Chemical Biology 2005; 9:656–664.