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DENDRIMER MULTIFUNCTIONAL NANO-DEVICE: A REVIEW

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ABSTRACT

A dendrimer is described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. The unique properties of dendrimers such as uniform size, high degree of branching, water solubility, multiagency, well-defined molecular weight and available internal cavities make them attractive for biological and drug-delivery applications. These artificial macromolecules may be synthesized to reach the size of nano objects having dimensions similar to proteins. Recently dendrimers have successfully proved themselves as promising nanocarriers for drug delivery because they can render drug molecules a greater water-solubility, bioavailability, and biocompatibility. These features have made their application in pharmaceutical, nanotechnology and medicinal chemistry particularly attractive. In addition 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 dendrimers. Commercialization of dendrimers is now forthcoming. The present review briefly describes about dendrimer synthesis, types of dendrimers with different functionalities, properties various importance and their potential applications in pharmaceutical and other different field.

INTRODUCTION: In earlier time polymer technologies were focused mainly on linear polymers. But now a days highly branched polymers have been potentially used in various pharmaceutical and biomedical fields to improve the various parameters of drug (like to target drug molecule, solubilization, to increase bio-availability), properties of branched macromolecules are quite different from conventional polymers. The unique structural features of dendritic and hyper branched macromolecules have number of chains whose ends combined with a high degree of branching which leads to a variety of new physical properties when compared with traditional linear polymers.

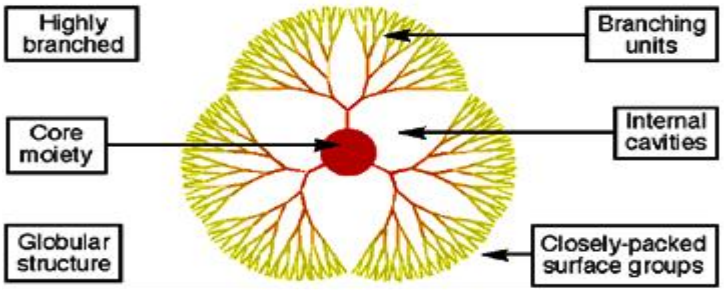

FIG. 1: DENDRITIC STRUCTURE

It offers a plenty of advantages compared to other architectural forms of polymers that have been used in drug delivery systems [1, 2, 52]. Dendrimer have narrow polydispersity, nanometer size range, which can allow easier passage across biological barriers (e.g. small enough to undergo extravasations through vascular endothelial tissues).

Binding groups in the interior of dendrimers are called endoreceptors (host-guest can take place either in the interior) or groups involved in complexation chemistry on the periphery of the dendrimers are called exoreceptors (On the periphery of the dendrimer). Macromolecular architectures of dendrimer provide unique nanoscopic shapes and surfaces which opens the door for either sub-nanoscopic reagents or nanoscopic reagents (e.g. antibodies, DNA etc.) to perform reactions.

"A dendrimer is generally described as a macromolecule, which is characterized by its dendritic and hyper branched 3D structure that offers a high degree of surface functionality and versatility." Dendrimers have often been referred to as the "Polymers of the 21st century" [4] Dendrimer chemistry was first introduced in 1978 by Fritz Vogtleand coworkers. He synthesized the first "cascade Molecules". In 1985, Donald A. Tomalia synthesized the first family of dendrimer.

It is originated from two Greek words, first is Dendron, means "tree" and second is meros means "part". At that time another work reported by, Newkome's group independently synthesised similar macromolecules i.e., called them *arborols* which comes from the Latin word 'arbor' also meaning a "tree". The term *cascade molecule* is also used, but *dendrimer* is the best established one. Due to their versatility character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.

Components of a Dendrimer Structure: It is the hyper branching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the branching points. The number of branching points when going from the core towards the dendrimer surface is the generation number. That is a dendrimer having five branching 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 *e.g*. a 5th generation polypropyleneimine is abbreviated to a "G5-PPI-" dendrimer.

The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented here "G0". The core structure thus presents no focal points, as hydrogen substituent's are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted half-generations; a well-known example is the carboxylic acid-terminated PAMAM dendrimer

Shell: Dendrimers consist of a series of chemical shells built on a small core molecule. Each shell consists of two chemicals, always in the same order. It is the homo-structural spatial segment between the focal points, the ''generation space''. The ''inner shells are generally PAMAM dendrimer with the main architectural components (a) core (b) interior and (c) surface. The outer shell is the space between the surface and the last outer branching point. There is varying number of pincers available at outer shell of dendrimers created by the last focal point before reaching the dendrimer surface.

End-Group: It is also called terminal group or surface group of dendrimers. Dendrimer which terminated by amine end-group is called ''amino-terminated dendrimers'' (**Fig. 2**).

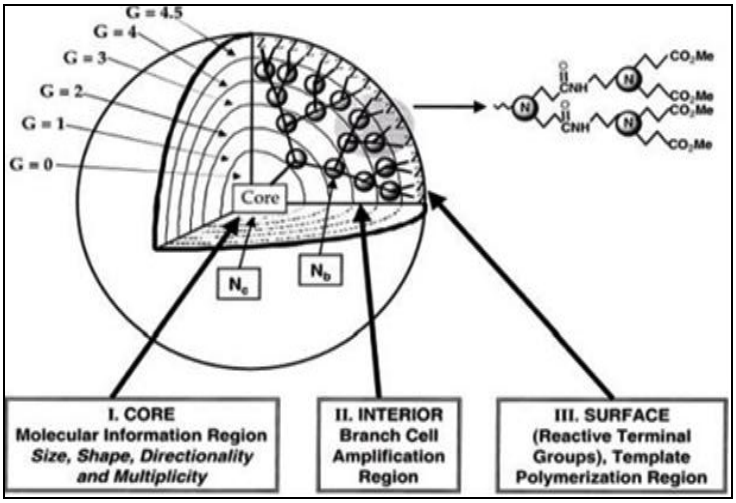

FIG. 2: THREE DIMENSIONAL PROJECTION OF DENDRIMER CORE-SHELL ARCHITECTURE FOR G= 4.5 PAMAM DENDRIMER WITH PRINCIPAL ARCHITECTURAL COMPONENTS (I) CORE, (II) INTERIOR & (III) SURFACE

Types of Dendrimers: A rapid development of this new kind of polymer has been possible and a variety of dendritic scaffold has become accessible with defined nanoscopic dimensions (3-5 nm) and discrete number of functional end groups. The first dendritic structures that were exhaustively investigated and that received widespread attention were Tomalia's PAMAM (poly amidoamine) dendrimers and "Newkome's arborol" systems.

PAMAM Dendrimer: Polyamidoamine dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents using a reiterative sequence consisting of a double Michael addition of methyl acrylate to primary amino group followed by amidation of resulting carbomethoxy intermediate with a large excess of ethylenediamine Products up to generation [5] 10 (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 star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

PAMAMOS Dendrimers: These dendrimers prepare with nanoscopic PAMAM and OS domains and useful for the preparation of honeycomb like network. It consists of hydrophilic, nucleophilic polyamidoamine interiors and hydrophobic organosilicon (OS) exteriors. Compositional variety of the resulting dendrimers is achieved by variation of the generation of PAMAM precursor and the type and functionality of the organosilicon reagent. A range of different PAMAMOS dendrimers can be obtained having

a) Different number of PAMAM branch cell layers in their interiors,
b) One or more layers of OS branch cells in their exteriors,
c) A variety of inert (e.g., trimethylsilyl or trimethylsiloxy) or reactive (e.g., alkoxysilyl, vinylsilyl, or vinylsiloxy) end-groups, and (d) different relative amounts of these end-groups.

Hybrid Dendrimers: It is a combination of hybrid block or graft copolymer forms of linear and dendritic polymers. The small dendrimer segment coupled to multiple reactive chain ends provides an opportunity to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers.

Peptide Dendrimers and Glycodendrimers: Dendrimers incorporating amino acids as branching or core units and peptide on surface of the traditional dendrimer framework both defined as 'peptide dendrimers'. Recent progresses in peptide and glycopeptides chemistry make the preparation of peptide and glycopeptides dendrimers of acceptable purity, with designed structural and immunochemical properties reliable. New methodologies using unprotected peptide building blocks have been developed to further increase the possibilities of their design and improve their preparation and separation. Glycodendrimers are following types.

(a) Carbohydrate-coated;

(b) Carbohydrate centered

(c) Fully carbohydrate-based.

The sophisticated design of peptide and glycopeptides dendrimers has led to their use as antigens and immunogens, for serodiagnosis and other biologically relevant field like study of protein, carbohydrate interaction that are in many intercellular recognition events. And also use to effectively evaluate protein – carbohydrate interaction, formulation of gels, targeting of MRI contrast agents; gene and drug delivery systems are some of the areas where these dendrimers are beneficial.

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

TECTO Dendrimers: Tecto-dendrimers formed by a core dendrimer, which may or may not contain the therapeutic agent, surrounded by dendrimers. In

which surrounding dendrimers are of several types, each type designed to perform a function necessary to a smart therapeutic nanodevice in various pharmaceutical fields [6].

Liquid Crystalline Dendrimers: There has been an increasing interest in the field of liquid crystalline dendrimers. Such a fast development is, among other things, driven by the multiple possibilities offered by combining the mesomorphic properties of single mesogenic subunits with the supermolecular and versatile architectures of dendrimers to yield a new class of highly functional materials.

They consist of mesogenic (liq. crystalline) monomers e.g. mesogen Functionalized carbosilane dendrimers. Functionalization of end group of carbosilane dendrimers with 36 mesogenic units, attached through a C-5 spacer, leads to liquid crystalline dendrimers that form broad smetic (A phase in the temperature range of 17–130^{o}C). The induction and the control of the mesomorphic properties (phase type and stability) in dendrimers can be achieved by a dedicated molecular design which depends on the chemical nature and structure of both the functional groups and the dendritic matrix.

In particular, the intrinsic connectivity of the dendrimer such as the multivalency of the focal core and the multiplicity of the branches, both controlling the geometrical rate of growth, or the dendritic generation, plays a crucial role and influences at various stages the subtle relationships between the supermolecular structure and the mesophase structure and stability.

Chiral Dendrimers: The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Chiral, nonracemic dendrimer with well-defined stereochemistry is particularly interesting subclass, with potential applications in asymmetric catalysis and chiral molecular recognition.

TABLE 1: WORK DONE ON VARIOUS DRUG MOLECULES UTILIZING DENDRIMERS

Drug	Dendrimers used	References
Anthracene	Polyether	Hawaker *et al*., 1993
Indomethacin	PEG polyether dendrimer	Kwon *et al*., 1997
Ibuprofen	PAMAM	Milhem *et al*., 2000
Adriamycin	PEGylated PAMAM	Kojima *et al.,* 2000
Methotreaxte	PEGylated PAMAM	Kojima *et al*., 2000
Methotreaxte	PAMAM	Khopade *et al*., 2002
Paclitaxel	Polyglycerol	Ooya *et al.*, 2003
Salicylic Acid	OH-terminated PAMAM	Beezer *et al*., 2003
5-Flurouracil	PEGylated PAMAM	Bhadra *et al*., 2003
Proflavine	Amphiphilic	Vutukuri *et al*., 2004
Indomethacin	Amine, hydroxyl & ester terminated PAMAM	Chauhan *et al*., 2004
Propranolol	PAMAM ana lauryl sulphate	D'Emanuel *et al*., 2004
Nifedepine	Amine and ester terminated PAMAM	Devarakonda *et al*., 2004
Naproxen	PAMAM	Yiyun *et al*., 2005
Nicotinic Acid	PAMAM	Yiyun *et al*., 2005
Diclofenac, Mefanamic Acid, 5- ASA	Citric Acid PEG PAMAM	Namazi *et al*., 2005
Artemether	PEGylated lysine	Bhadra *et al*., 2005
Ketoprofen	PAMAM	Yiyun *et al*., 2005
Flurbiprofen	PAMAM	Asthana *et al.,* 2005
Naproxen	PAMAM	Najlah *et al*., 2006
Rifampicin	Monosylated PPL	Kumar *et al*., 2006
Dimethoxy-curcumine	PAMAM	Markatou *et al*., 2007
Methylthiozole tetrazolium	PAMAM	Dipak *et al*., 2008
8-methoxypsoraline	PAMAM	Borowska *et al*., 2010
Ibuprofen	PAMAM	Yunus *et al*., 2010

Advantages of Dendrimers: Dendrimers are hyperbranched, globular, monodisperse, nanometric polymeric architecture, having definite molecular weight, shape, and size (which make these an inimitable and optimum carrier molecule in pharmaceutical field). Dendritic architecture is having immense potential over the other carrier systems, particularly in the field of drug delivery because of their unique properties, such as structural uniformity, high purity, efficient membrane transport, high drug pay load, targeting potential, and good colloidal, biological, and shelf stability.

Despite their enormous applicability in different areas, the inherent cytotoxicity, reticuloendothelial system (RES) uptake, drug leakage, immunogenicity, and hemolytic toxicity restricted their use in clinical applications, which is primarily associated with cationic charge present on the periphery due to amine groups. To overcome this toxic nature of dendrimers, some new types of nontoxic, biocompatible, and biodegradable dendrimers have been developed (e.g., polyester dendrimer, citric acid dendrimer, arginine dendrimer, carbohydrate dendrimers, etc.).

The surface engineering of parent dendrimers is graceful and convenient strategy, which not only shields the positive charge to make this carrier more biomimetic but also improves the physicochemical and biological behavior of parent dendrimers. Thus, surface modification chemistry of parent dendrimers holds promise in pharmaceutical applications (such as solubilization, improved drug encapsulation, enhanced gene transfection, sustained and controlled drug release, intracellular targeting) and in the diagnostic field.

Development of multifunctional dendrimer holds greater promise toward the biomedical applications because a number of targeting ligands determine specificity in the same manner as another type of group would secure stability in biological milieu and prolonged circulation, whereas others facilitate their transport through cell membranes. Therefore, as a consequence of ideal hyperbranched architecture and the biocompatible nature of engineered dendrimers, their utilization has been included in the scope of this review, which focuses on current surface alteration strategies of dendrimers for their potential use in drug delivery and explains the possible beneficial applications of these engineered dendrimers in the biomedical field.

Dendrimers offers various advantages over other polymers:

- 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 M.W) that allows them to target tumor cells more effectively than small molecules.
- The advantage of dendrimers is that they can be synthesized and designed for specific applications. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal (Petri, Majoros and Baker. 2002)

Properties of Dendrimers:

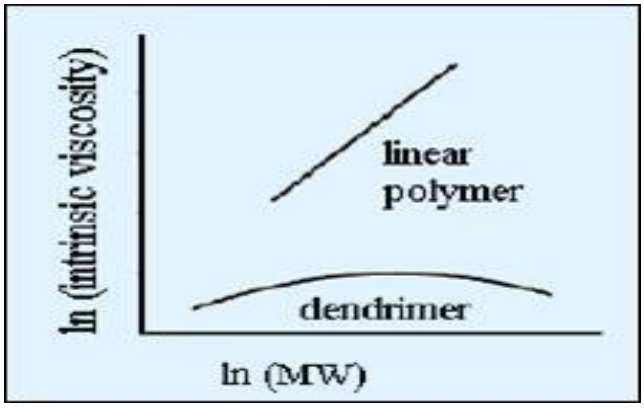

FIG. 3: CORRELATION BETWEEN INTRINSIC VISCOSITY AND MOLECULAR WEIGHT

TABLE 2: PROPERTIES OF DENDRIMER AND LINEAR POLYMERS

Property	Dendrimers	Linear Polymers
Structure	Compact, Globular	Not compact
Synthesis	Careful & stepwise growth	Single step poly-condensation
Structural control	Very high	Low
Architecture	Regular	Irregular
Shape	Spherical	Random coil
Crystallinity	Non-crystalline, amorphous materials - lower glass temperatures	Semi-crystalline/ crystalline materials - Higher glass temperatures
Aqueous solubility	High	Low
Nonpolar solubility	High	Low
Reactivity	High	Low
Compressibility	Low	High
Polydispersity	Monodisperse	Polydisperse

Properties of Dendrimers:

Polyvalency: Dendrimers provide many interactions (Polyvalency) as they coordinate to materials. Polyvalency results from the outward presentation of reactive groups on the dendrimer nanostructure exterior. This creates more connections between surfaces and bulk materials for applications such as adhesives, surface coatings, or polymer cross-linking. Simultaneously, these functional groups can participate in multiple interactions with receptors on biological structures like cell membranes and viruses [7]. The polyvalency of a dendrimer glucosamine conjugates is also thought to be responsible for the ability of these molecules to efficiently inhibit scar-tissue formation. In preliminary animal studies, the bifunctional dendrimer increased the long-term success rate of glaucoma surgery from 30% to 80% [8].

As Solubility Enhancers:

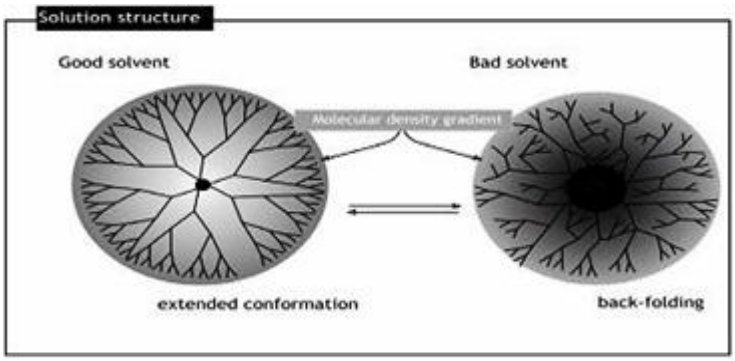

FIG. 4: SOLUTION STRUCTURE

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties.

Dendrimers having a hydrophobic core and a hydrophilic surface layer have been termed unimolecular micelles. Unlike traditional micelles, dendrimers do not have a critical micelle concentration. This characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure at all concentrations of dendrimers [9].

A hydrophilic-hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-flurouracil, a water-soluble anti-tumor drug. After phospholipid coating of the dendrimer-fatty acid macromolecule, oral bioavailability in rats of 5-flurouracil was nearly twice the level of free 5-flurouracil. Dendrimer-based carriers could offer the opportunity to enhance the oral bioavailability of problematic drugs. Propranolol, conjugated to surface modified G3 PAMAM dendrimer, the solubility of propranolol increased by over two orders of magnitude. Thus, dendrimer nano-carriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

Nanoscale Size and Shape: The diameter of the generation 1-10 with ethylenediamine core increases from 1.1 to 12.4nm within the PAMAM dendrimer

family [10]. The shape is very important parameter, as it allows the defined placement of functions not only on the dendrimer surface but also inside the dendritic scaffold. The PAMAM dendrimers of lower generation (G0–G3) with ethylenediamine core have ellipsoidal shapes, whereas the PAMAM dendrimer of higher generation (G4–G10) have roughly spherical shapes. X-ray study on dendrimer aggregates have been revealed that the molecular shape of the lower to higher generations becomes increasingly globular in order to spread out the larger molecular structure with a minimal repulsion between the segments [11]. These fundamental properties have in fact lead to their commercial use for gene therapy, immunodiagnostics and variety of other biological applications [12].

Monodispersity: Convergent process gives the monodisperse molecules as determined by mass spectrometry. That is the reasons by Tomalia convergently produced dendrimers are probably the most precise synthetic macromolecules that exist today [13]. However, mass spectroscopy has shown that dendrimers produced by divergent method are remarkably monodisperse for earlier generation (G= 0 - 5) (Tomalia 1993). Monodispersity offers researchers the possibility to work with a tool for well-defined scalable sizes. The two factors affects the degree of monodispersity includes,

- Dendrimer bridging
- Incomplete removal of ethylenediamine at each of the generation sequences [14]. This latter factor at any point in dendrimer growth will function as an initiator core to produce 0.5 generation and subsequent generation dendrimers that leads to polydispersity. Ethylenediamine can be effectively removed from the lower generation dendrimers by simple vacuum distillation at lower temperature and from higher generation dendrimers (i.e. G> 4) by special techniques like azeotropic (n-butanol) and wiped film distillation [15].

Biocompatibility of Dendrimers: Duncan and co-workers have investigated the relationship between structure and biocompatibility of PAMAM, poly (propyleneimine), poly (ethylene oxide) grafted carbosilane dendrimers with cationic (NH_2-terminated) and anionic (COONa-terminated) dendrimers in vitro. They have reported that, regardless of structure, cationic dendrimers were generally more haemolytic and cytotoxic effect at even relatively low concentration in comparison to anionic dendrimers. They have also reported increase in the haemolysis with increase in the generation [16]. One more study reported that anionic PAMAM dendrimers have shown a significantly lower cytotoxicity than cationic dendrimer using Caco-2 cells [17]. Hydroxy- or methoxy-terminated polyester dendrimers have been reported to have low toxicity in both in vitro and in vivo studies. During *in vitro* study, at high concentration, these dendrimers have induced some inhibition of cell growth but no increase in cell death was observed. Upon injection into mice, no acute or long-term toxicity problems observed. The results make these new dendritic motifs promising candidates for drug-delivery devices [18].

Physicochemical Properties of Dendrimers: It was already suggested that nano-sized structure of higher generation dendrimers would serve as synthetic mimics of proteins. The hyperbranched structure of the dendrimer is less compact than a protein, i.e. interior is not packed as efficiently as in typical proteins, and structure of the dendrimer provides a highly multivalent surface, exposing a much higher number of functional groups on the surface compared to proteins of similar molecular size [19].

The use of dendrimers as protein mimics has been encouraged scientists to investigate the physicochemical properties of dendrimers in comparison to proteins shows that dendrimers, similar to protein, can adapt “native” (e.g. tighter) or “denaturated” (e.g. extended) conformations dependent on the polarity, ionic strength and pH of the solvent.

Amino terminated PPI and PAMAM dendrimers (that is the dendrimers having basic surface groups as well as a basic interior) at the low pH region shows the extended conformation due to electrostatic repulsion between the positively charged ammonium groups. At neutral pH back folding occurs which may be due to the hydrogen bonding between the unchanged tertiary

amines in the interior and the positively charged surface amines. At pH ≥10 conformation has a higher degree of back folding so dendrimer acquires a more spherical (globular) structure, that all because of the weak "inter-dendron" repulsive forces. In comparison with carboxylic acid terminated PPI dendrimers, small angle neutron scattering (SANS) and NMR measurements shows that at pH 2 the dendrimer core has the most extended conformation due to the electrostatic repulsion between the positively charged protonated tertiary amines.

At pH 6 slight back folding occurs as a result of attractive Coulomb interactions between the negatively charged surface carboxy-groups and the positively charged tertiary amines in the inner shells of the dendrimer. While at pH 11 the electrostatic repulsion between the negative charged forces the surface groups apart from which gives amore extended conformation with a highly expanded surface area [20].

Polarity of the solvent greatly influences the structure of the dendrimer. NMR studies performed on PPI dendrimer revealed that an polar solvent such as benzene will favor polar intramolecular interactions (e.g. hydrogen bonding) resulting in back-folding of the dendrimer arms into the dendrimer interior, whereas the increased acidity of chloroform, will increase salvation of the dendrimeric structure via hydrogen bond donation to the interior tertiary amines resulting in a more extended conformation of the dendrimer [21]. At high ionic strength (high concentration of salts) charged PPI dendrimers favors a contracted conformation of dendrimers with a high degree of back-folding. In contrast at low salt concentration, the repulsive forces between the charged dendrimer segments result in an extended conformation [22].

Synthesis of Dendrimers: The first was introduced by Tomalia, called as "divergent method" in which growth of dendrimers originates from a core site. This approach involves assembling monomeric modules in a radial, branch-upon-branch motif according to certain dendritic rules and principles [23]. The second method, pioneered by Hawker and Frechet follows a "convergent growth process" [24], in which, several dendrons are reacted with a multifunctional core to obtain a product.

Divergent Dendrimer 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 [25]. 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;

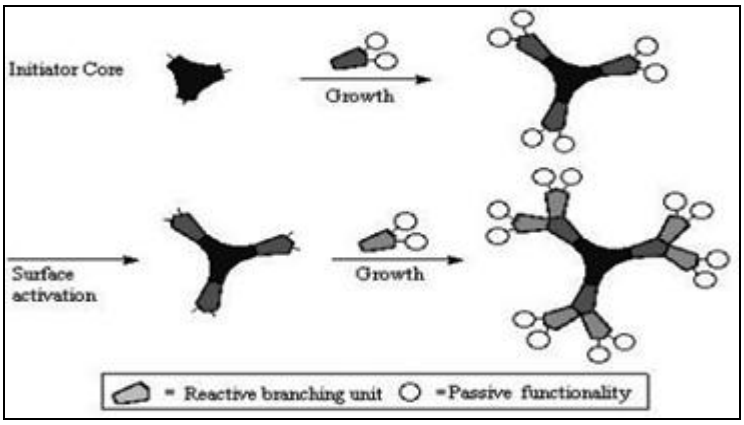

FIG. 5: DIVERGENT DENDRIMER GROWTH METHOD

Convergent Dendrimer Growth: 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.

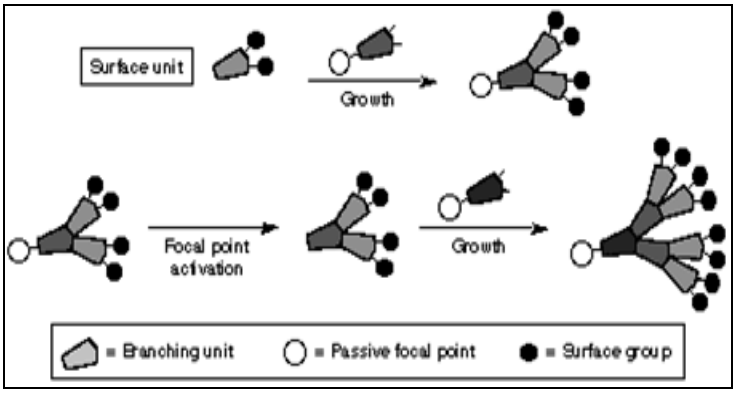

FIG. 6: CONVERGENT DENDRIMER GROWTH

The advantages of convergent growth over divergent growth stem from the fact that only two simultaneous reactions are required for any generation-adding step.

Most importantly, this protocol makes the purification of perfect dendrimers simple. There are also certain other advantages associated with convergent growth. The growth reactions do not have to be so stringently efficient, and it becomes possible to introduce subtle engineering into the dendritic structure. Convergent syntheses are not without their own shortcomings, however. The number of steps required to build up a large structure is not reduced compared with the divergent approach, yet a great deal more starting material is required. The convergent methodology also suffers from low yields in the synthesis of large structures. Dendritic wedges of higher generations encounter serious Stearic problems in the reactions of their 'focal points'. Multiplications of the number of terminal surface groups from 48 to 250 in one step. This synthesis requires minimum volume of solvent allow facile purification and usefulness in coming years.

Applications of Dendrimers: Dendrimers as a carrier for drug delivery Dendrimers have narrow polydispersity; nanometer size range of dendrimers can allow easier passage across biological barriers. All these properties make dendrimers suitable as host either binding guest molecules in the interior of dendrimers or on the periphery of the dendrimers.

- **Dendrimers in Transdermal Drug Delivery:** Recently dendrimers have found applications in transdermal drug-delivery systems. It provides slow release action and less fluctuation action. Generally, bioactive drugs have hydrophobic moieties in their structure, resulting in low water solubility that inhibits efficient delivery into cells. Dendrimers designed to be highly water soluble 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.

  Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) could be improving the drug permeation through the skin as penetration enhancers [26]. The model drugs Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies. In vitro permeation studies on excised rat skin showed 3.4 times higher permeation of Ketoprofen from Ketoprofen-dendrimer complex than that from 2mg/ml Ketoprofen suspended in normal saline. Similarly, a 3.2 times higher permeated amount was observed with Diflunisal-dendrimer complex. Anti-nociception effect of drugs was studied on mice, results showed that Ketoprofen-dendrimer complex reducing writhing activity during the period of 1-8 h after Transdermal administration, while pure Ketoprofen suspension at the equivalent dose of Ketoprofen significantly decreased number of writhing between 4 and 6 h after drug was transdermally given [27].

  Chauhan *et al*., investigated transdermal ability of PAMAM dendrimers by using indomethacin as the model drug for study. In vitro permeation studies showed increase in the steady-state flux as increase in concentration of all three types G4-NH2, G4-OH and G-4.5 PAMAM dendrimers. For the in vivo pharmacokinetic and pharmacodynamic studies, indomethacin and dendrimer formulations were applied to the abdominal skin of the Wistar rats and results showed that effective concentration could be maintained for 24 h in the blood with the G4 dendrimer–indomethacin formulation. Therefore, data suggested that the dendrimer–indomethacin based transdermal delivery system was effective and might be a safe and efficacious method for treating various diseases [14].

- **Dendrimers in Oral Drug Delivery:** It is by far the most convenient administration route with good patient compliance, especially in the patient's opinions. Along with these benefits, there are also some defects of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes [28]. D'Emanuele and his research group [17] investigated effect of dendrimer generation and conjugation on the cytotoxicity, permeation and transport mechanism of PAMAM dendrimer and surface-modified cationic PAMAM dendrimer using monolayers of the human colon adenocarcinoma cell line, Caco-2.

As increase in the concentration and generation, there was increase in the cytotoxicity and permeation of dendrimers. While reduction in cytotoxicity observed by conjugation with lauryl chloride. Modified dendrimers also reduced transepithelial electrical resistance (TEER) and significantly increased the apparent permeability coefficient (Papp).

In another study of transepithelial permeability of naproxen, a low solubility model drug was investigated [29]. The stability of these G0 PAMAM conjugates in 50% liver homogenate was compared to that in 80% human plasma showed the lactate ester linker gave prodrug of high stability in plasma with slow hydrolysis in liver homogenate; such conjugates may have potential in controlled release systems, while using diethylene glycol as a linker gives conjugate that showed high chemical stability, but readily released drug in plasma and liver homogenate. Investigators have lastly concluded that dendrimers conjugate with drug could reduce the effect of intestinal P-gp on drug absorption of propranolol and many other orally administered drugs [30].

- **Dendrimers in Ocular Drug Delivery:** It is generally agreed that the intraocular bioavailability of topically applied drugs is extremely poor. These results mainly due to drainage of the excess fluid via nasolacrimal duct and elimination of the solution by tear turnover. Several research advances have been made in ocular drug-delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome some of these disadvantages. Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable [30].

  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 [31].

- **Dendrimers in Pulmonary Drug Delivery:** Dendrimers have been reported for pulmonary drug delivery also [32]. During one study, efficacy of PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin was Studied by measuring plasma anti-factor Xa activity, and by observing prevention efficacy of deep vein thrombosis in a rodent model. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40%, while G2.5 PAMAM, a half generation dendrimers, containing negatively charged carboxylic groups had no effect.

  Formulations did not adversely affect mucociliary transport rate or produce extensive damage to the lungs. So the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery [32]. Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid. Membrane associated high-affinity folate receptors are folate-binding proteins that are over expressed on the surface of different types of cancer cells (e.g. ovarian). PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively.

  Further, these two molecules are linked with complementary oligonucleotides. DNA-assembled nanoclusters were evaluated in vitro which helps in detecting tumor cell-specific binding and internalization. These DNA-assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics [33].

  Patri and co-workers have investigated that complexing a drug with dendrimer as an inclusion complex improves its solubility in water, a cleavable, while covalently linked dendrimer conjugate is better for targeted drug delivery because it does not release the drug prematurely in biological conditions. They reported less cytotoxic effect with the covalently linked dendrimer [34].

- **Dendrimers for Controlled Release Drug Delivery:** Frechet and co-workers have prepared polyaryl ether dendrimers containing dual functionality on the surface. One is used to attach polyethylene glycol (PEG) units on the surface to improve water solubility and the other one is utilized to attach hydrophobic drug molecules. They have also synthesized a series of dendritic unimolecular micelles with a hydrophobic polyether core surrounded by a hydrophilic PEG shell for drug encapsulation. A third-generation micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control [34].

  PEG-2000 was conjugated to generation G3 PAMAM dendrimers with varying degree of substitution. Methotrexate drug was encapsulated (loaded) to the prepared conjugates and investigated for drug release in a dialysis bag. The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to unencapsulated drug. Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM dendrimers.

  Prepared dendrimer complexes observed that loaded drug displayed initial rapid release (more that 40% till 3rd hour) followed by slow release. The dendritic formulation showed 2-fold and 3-fold increased in mean residence time and terminal half-life, respectively, as compared to free drugs [35].

- **Dendrimers in Gene Delivery:** Because of their immunogenicity, dendrimers are extensively used as non-viral vector for gene delivery. The use of dendrimers as gene transfection agents and drug-delivery devices have been extensively reviewed part [36]. The ability of cationic dendrimers to deliver DNA or RNA has been reviewed previously. Besides of that some research recently indicated that dendrimer based gene delivery system also have significant potential in clinical trials. Kukowska-Latallo *et al.*, reported that intravenous administration of G9 PAMAM dendrimer-complexed pCF1CAT plasmid could result in high level of gene expression in the lung tissues of rats.

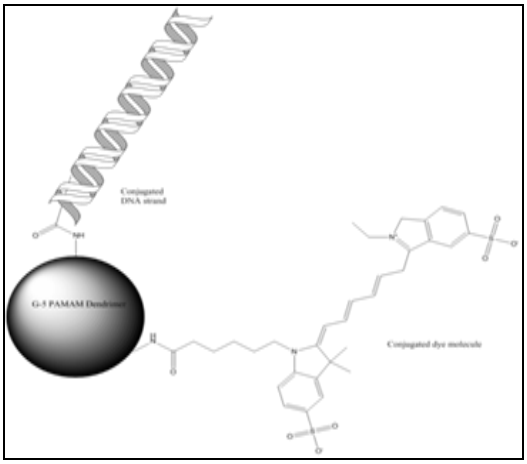

FIG. 7: SCHEMATIC OF A G-5 PAMAM DENDRIMER CONJUGATED TO BOTH A DYE MOLECULE AND A STRAND OF DNA

It enhances the transfection efficiency and expression pattern of dendrimers [37]. It was anticipated that the hydrophobic components would mimic the membrane transfection ability of natural phospholipids such as dioleoyl phosphatidylethanolamine (DOPE) and enhance membrane penetration. These constructs forms complexes with DNA and, in case of the G= 2-4 dendrimers, were able to cross cell membranes and efficiently deliver DNA [9].

Polycationic dendrimers also studied with a different cell lines for ability to transfect DNA and toxicity. In the result, some of polycation-DNA complexes were less toxic than lipid-DNA systems [38]. Glycoplexes are used to target to the specific cells and/or to increase gene transfer activity. For example, a galactosylated polyethyleneimine (PEI) has high transfection efficiency to hepatocyte expressing asialoglycoprotein receptor.

- **Dendrimers as Imaging Agents:** The first in vivo diagnostic imaging applications using dendrimer-based MRI contrast agents were demonstrated in the early 1990s by Lauterbur and colleagues [39].

  In comparison with the commercially available small-molecule agent (Magnevist, Schering AG), the dendrimer-based reagents exhibited blood pool properties and extraordinary relaxivity values when chelated gadolinium groups (Magnevist). These generation dependent, dramatic enhancements of MRI contrast properties were some of the first examples of a 'dendritic effect' [40].

Gadolinium is an FDA-approved contrast agent for MRI which provides greater contrast between normal tissue and abnormal tissue in the brain and body. It is safer than the iodine type contrast used in CT scans and also non-radioactive and is rapidly cleared by kidneys. The largest MRI contrast agent G5 with 64 Gd(III) ions gives lowest concentration detection limit would make G5 potentially the best dendritic MRI contrast agent [41].

Dendrimer applications in various fields: Countless applications involving dendrimers are being researched worldwide. The following is an extensive list of the most common dendrimer applications.

Power/Energy:

- Catalytic agent

Healthcare/Medical:

- Cellular Transport
- Artificial cells
- Diagnostics and analysis
- Targeted delivery (e.g. protein, antibody and anti-inflammatory; nanoparticles,
- Radionucleides, fluorescent markers, etc.)
- MRI contrast agents (e.g. organ, vascular and tumor imaging)
- Transfection reagents, DNA-carriers
- Protein / enzyme mimics or modeling
- Manufacture of artificial bones
- Development of topical microbicide creams; antimicrobial, antiviral (e.g. for use against HIV) and antiparasitic agents
- Biomedical coatings (e.g. for artificial joints)
- Novel polyvalent dendrimer-based drugs
- Artificial antibodies and biomolecular binding agents, e.g. anti-infection and toxin treatment for SARS / bird flu (especially blocking the cytochine storm),
- Biowarfare, antibiotic-resistant drugs, etc.

Engineering:

- Molecular weight and size standards
- Chemical / biological sensors & detectors
- Carbon fiber coatings and ultra thin film
- Polymer and plastics additives (e.g. for lowering viscosity, increasing stiffness, incorporating dyes, compatibilizers, etc.) Creation of foams (i.e. synthetic zeolites or insulating material)
- Building blocks for nanostructured materials

Consumer Goods:

- Ink / laser-printing toners
- Dyes and paints
- Industrial adhesives
- Manufacture of nanoscale batteries and lubricants

Environmental:

- Decontamination agents (trapping metal ions)
- Ultrafiltration

Electronics / Optoelectronics:

- Molecular electronics for data storage
- 3-D optical materials
- Light-harvesting systems
- OLEDs (i.e. flat panel displays and other light emission applications)
- Quantum dots
- Liquid crystals
- Printed wire boards
- Low-k materials (i.e. insulation materials)

Overview of applications in 2010: The following figure is an overview of the expected state of development of different applications of dendrimer in year 2010. After five years many more applications will have come into fruition. The text and the figures presented in this section are mainly based on the input given by the participants in the Delphi panel. A good number of the potential applications currently considered would most probably be either in the applied R&D phase or already approaching the first commercial applications.

Future concepts that will enter the funnel of applications in 2010 include nanodevices. Applications that will remain in the basic R&D phases include multifunctional medical dendrimers (e.g. *tectodendrimers* - pioneer is James Baker of Michigan University and NanoBio). Basic to apply now (this is in 2005), it can be expected to approach first applications in 2010, but the basic research will also remain strong for many years.

Overview of applications in 2015: The following figure is an overview of the expected state of development of different applications of dendrimers in year 2015. The text and the figures presented in this section are mainly based on the input given by the participants in the Delphi panel.

By 2015 many applications currently in development will be actual markets and currently still wild ideas may be ready to move to the market. Certain specific electronic and medical applications, however, might take even further time to develop. In the case of health-related applications, this might be due to the need to carry out lengthy clinical trials and the need for relevant administration approval.

Future research ideas include nanodevices, which may enter the applied research phase by 2015.

CONCLUSION: Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

Future Prospect: Dendrimer drug delivery systems are increasingly viewed as an advantageous solution for bioactive like drugs and gene. They provide a platform for the attachment of drugs or genes and their release through several mechanisms. Scientists have explored the use of dendrimers for various applications in oral, transdermal, ophthalmic, and gene delivery. Although dendrimer drug delivery requires attention to certain manufacturing and biological considerations to be successful. Boosting of commercial applications of dendrimer technology will provide strength for its usefulness in coming years.

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