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DENDRIMER - FOR NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT:

It is a highly branched synthetic polymer and consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped or generational structure with precise molecular weights, diameters in the 2 to 10 nm range size, its unique architectural design, high degree of branching, multivalency, globular structure and representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". In these formative years of nanotechnology, one of the most frequently seen names in the scientific literature is a class of polymerized macromolecules that carry the potential to provide the most exquisitely tailored forms and functions ever realized outside of nature. These polymerized macromolecules named as "dendrimers" are visualized as the polymers of 21st century. The term "dendrimer" is derived from the Greek words dendron, meaning tree and meros, meaning part. Dendrimers were introduced in 1980's by Donald A. Tomalia, scientific director of the Center for Biologic Nanotechnology at the University of Michigan. Ideally, these are perfectly monodisperse macromolecules with a regular and highly branched three-dimensional architecture. Think of a tree in which each of its branches divides into two new branches after a certain length. This continues repeatedly until the branches become so densely packed that the canopy forms a globe. In a dendrimer, the branches are interlinked polymerized chains of molecules, each of which generates new chains, all of which converge to a single focal point or core. In 1978, Fritz Vogtle and co-workers, introduced dendrimer chemistry and in 1985, Donald A. Tomalia, synthesized the first family of dendrimer. Dendrimers are repeatedly branched roughly spherical large molecules and possess well defined chemical structures. The word dendrimer comes from a Greek word which means to "tree". At the same time, Newkome's group independently reported synthesis of similar macromolecules. They called them arborols from the Latin word 'arbor' also meaning a tree. The other synonyms for dendrimer include cascade molecules. It is a highly branched synthetic polymer and consists of a monomer unit attached core, where a, leading to a monodisperse,

treelike, star-shaped or generational structure with precise molecular weights, diameters in the 2 to 10 nm range size, its unique architectural design, high degree of branching, multivalency, globular structure and representative of a new segment of polymer science, often been referred to as the "Polymers of the 21st century". Poor solubility, bioavailability, permeability, biocompatibility and toxicity can be overcome by dendrimers. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Dendritic polymers or dendrimers provide a route to create very welldefined nanostructures suitable for drug solubilisation applications, delivery of oligonucletide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular.

Structure of dendrimers:

Dendrimers are built from a starting atom, such as nitrogen, after a repeating series of chemical reactions, carbon and other elements was added into it; produce a spherical branching structure. As the process repeats, result is a spherical macromolecular structure. Dendrimers possess three distinguished architectural components, namely a central core which is either a single atom or an atomic group, Generation in which branches emanating from the core composed of repeating units, which is radially in position and many terminal functional group generally located in the exterior of the macromolecule.5,6 Structure of dendrimer as shown in (Fig. 1).

A dendrimer is typically symmetric around the core, and often develops a three dimensional morphology. In the view of polymer chemistry dendrimeres are perfect monodisperse macro molecules with regular highly branched three dimensional structures and consist of three architectural components like core,branches and end groups**.** 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 [9]. 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 The increasing branch density withgeneration is also believed to have striking effects on the structure of dendrimers. They are characterised by the presence of internal cavities and by a large number of reactive end groups. Dendritic copolymers are a specific group of dendrimers.

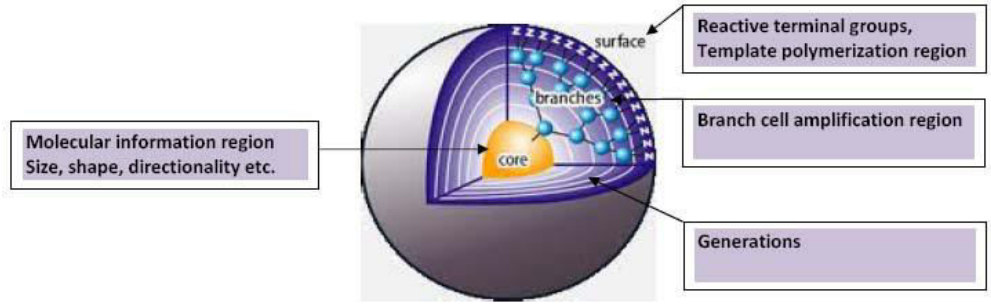

Figure 1: The Dendrimer Structure

There are two different types of copolymer

1. **Segment-block dendrimers** are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one poly functional core molecule.

2. **Layer-block dendrimers** consist of concentric spheres of differing chemistry. They are the result of placing concentric layers around the central core. Hawker and Freshet synthesized a segment-block dendrimer which had one ether-linked segment and two ester-linked segments. They also synthesized a layer-block dendrimer. The inner two generations were ester-linked and the outer three ether linked. The multi-step synthesis of large quantities of higher generation dendrimers requires a great effort. This was the reason why Zimmerman's group applied the concept of self-assembly to dendrimer Synthesis.

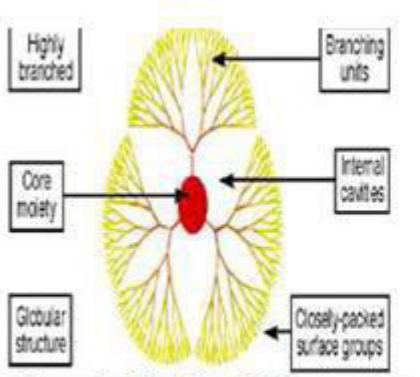

Figure 1: The Dendritic structure

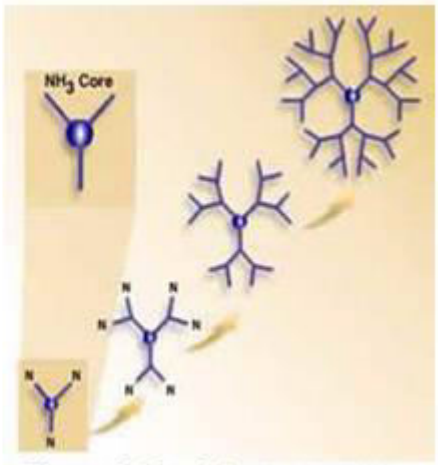

Figure 2: Dendrimer structure

They prepared a wedgelike molecule with adendritic tail in such a manner that six wedge-shaped subunits could self-assemble to form a cylindrical aggregate. This hexameric aggregate is about 9 nm in diameter and 2 nm thick. It has a large cavity in the centre. The six wedges are held together by hydrogen bonds between carboxylic acid groups and stabilised by Vander Waals interactions. However, the stability of the hexamer is affected by many factors. The aggregate starts to break up into monomers when the solution is diluted, when the aggregate is placed in a polar solvent like tetrahydrofuran (THF), and when the temperature is high. The hexamer's limited stability is due to its noncovalent nature.

Advantages of Dendrimers

Dendrimers offers various advantages over other polymers:

-Dendrimers have nanoscopic particle size range from 1 - 100 nm, which makes them less susceptible for reticulum endothelium uptake.

-They have lower polydispersity index, due to stringent control during synthesis. As the density of branches increases the outer most branches arrange themselves surrounding a lower density core in the form of spheres and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.

-Multiple functional groups are present on outer surface of dendrimers, 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 which allows them to target tumour cells more effectively than small molecules.

-They can be synthesized and designed for specific applications. Due to their feasible topology, functionality and dimensions, they are ideal drug delivery systems; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.

Types of dendrimers

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

   In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, electronics, photonics, chemical catalysis etc. And useful precursors for the preparation of honeycomblike networks with nanoscopic PAMAM and OS domains.

2. **Poly (amidoamine) dendrimers (PAMAM)**

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

3. Poly (Propylene Imine) dendrimers (PPI)

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary tris-propylene amines present in interior portion. It commercially available up to G5, and wide applications in material science as well as in biology.16 PPI dendrimers are available as AstramolTM.

4. Chiral dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.

5. Liquid crystalline dendrimers

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

6. Tecto dendrimer

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

7. Hybrid dendrimers

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

8. Multilingual Dendrimers

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

9. Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

10. Amphiphilic Dendrimers

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

11. **Peptide dendrimers**

Multiple Antigen Peptide dendrimers is a dendron-like molecular construct, use in biological applications, e.g. Vaccine and diagnostic research. Peptide dendrimers can be used as drug delivery, contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and sero diagnosis.

12. Frechet-Type Dendrimers

Frechet-Type Dendrimers 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.

PROPERTIES OF DENDRIMER

Monodispersity:

Dendrimers are the class of dendritic polymers that can be constructed with a well-defined molecular structure, i.e. being monodisperse, unlike to linear polymers. Monodispersity offers researchers the possibility to work with a tool for well-defined scalable size.

Nanoscale size and shape:

These fundamental properties have in fact lead to their commercial use for gene therapy, immunodiagnostics and variety of other biological applications.

Polyvalency:

Polyvalency shows 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 crosslinking. The product, a topical vaginal microbicide called Vivagel, prevents infection by HIV and other sexually transmitted diseases during intercourse takes advantage of dendrimers polyvalent properties.

Physicochemical properties of dendrimers:

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.

Biocompatibility of dendrimers :

In order to utilize dendrimers as biological agents, they have to fulfill certain biological demands. The dendrimer should be: nontoxic, non-immunogenic, able to cross biobarriers (biopermeable), able to stay in circulation for the time needed to have a clinical effect and able to target to specific structures. The cytotoxicity of dendrimers has been primarily evaluated in vitro; however, a few in vivo studies have been published. Dendrimers with positively charged surface groups are prone to destabilize cell membranes and cause cell lysis. For example, in vitro cytotoxicity, IC50 measurements (i.e., the concentration where 50% of cell lysis is observed) for poly (amidoamine) PAMAM dendrimers with amino surface revealed significant cytotoxicity on human intestinal adenocarcinoma, Caco-2 cells. Comparative toxicity studies on anionic (carboxylate-terminated) and cationic (amino-terminated) PAMAM dendrimers using Caco-2 cells have shown significantly lower cytotoxicity of the anionic compounds [16]. Furthermore, the cytotoxicity was found to be generation dependent with higher generation dendrimers being the most toxic, [17] some recent studies have shown that amino-terminated PAMAM dendrimers exhibit lower toxicity than more flexible linear polymers carrying amine groups, perhaps due to lower adherence of the rigid globular dendrimers to cellular surfaces. The degree of substitution as well as the type of amine functionality is important, with primary amines being more toxic than secondary or tertiary amines.Lower-generation PAMAM dendrimers possessing carboxylate surface groups show neither haemato-toxicity nor cytotoxicity at concentrations up to 2 mg/ml.

Immunogenicity

Immunogenicity is one of the crucial biological properties of the dendrimers. Studies performed on unmodified aminoterminated PAMAM dendrimers showing no or only weak immunogenicity of the G3–G7 Many dendrimer syntheses rely upon traditional reactions, such as the Michael reaction or the Williamson ether synthesis whilst others involve the use of modern dendrimers. However, later studies showed some immunogenicity of these dendrimers and found that modification of aminoterminated PAMAM dendrimers

with polyethylene glycol (PEG) chains reduces immunogenicity and gives longer lifetime in the blood stream in comparison to unmodified dendrimers.

SYNTHESIS OF DENDRIMERS

Synthetic methodology

The synthesis used for Dendrimer preparation permit almost entire control over the critical molecular design parameters such as size, shape, surface/interior chemistry, flexibility, and topology. Branching May either be present in the building blocks as is more often the case or it can be created as a function of the growth reaction.

1. **Divergent Method**:

In which growth of a Dendron (molecular tree) originates from a core site (Fig. 3). The 1980s, virtually all dendritic polymers were produced by construction from the root of the molecular tree. This approach involved assembling monomerric modules in a radial, branch-upon-branch motif according to certain dendritic rules and principles. This divergent approach is currently the preferred commercial route used by worldwide producers including Dendrimax (AnnArbor, MI, USA), DSM Fine Chemicals (Geleen, The Netherlands) and The Perstorp Group (Perstorp, Sweden).

(1) Convergent Method:

A second method that was pioneered by Fréchet and colleagues is the convergent growth process. It proceeds from what will become the Dendron molecular surface (i.e. from the leaves of the molecular tree) inward to a reactive focal point at the root (Fig. 3). This leads to the formation of a single reactive Dendron. To obtain a Dendrimer structure, several Dendrons are reacted with a multi-functional core to yield such a product.

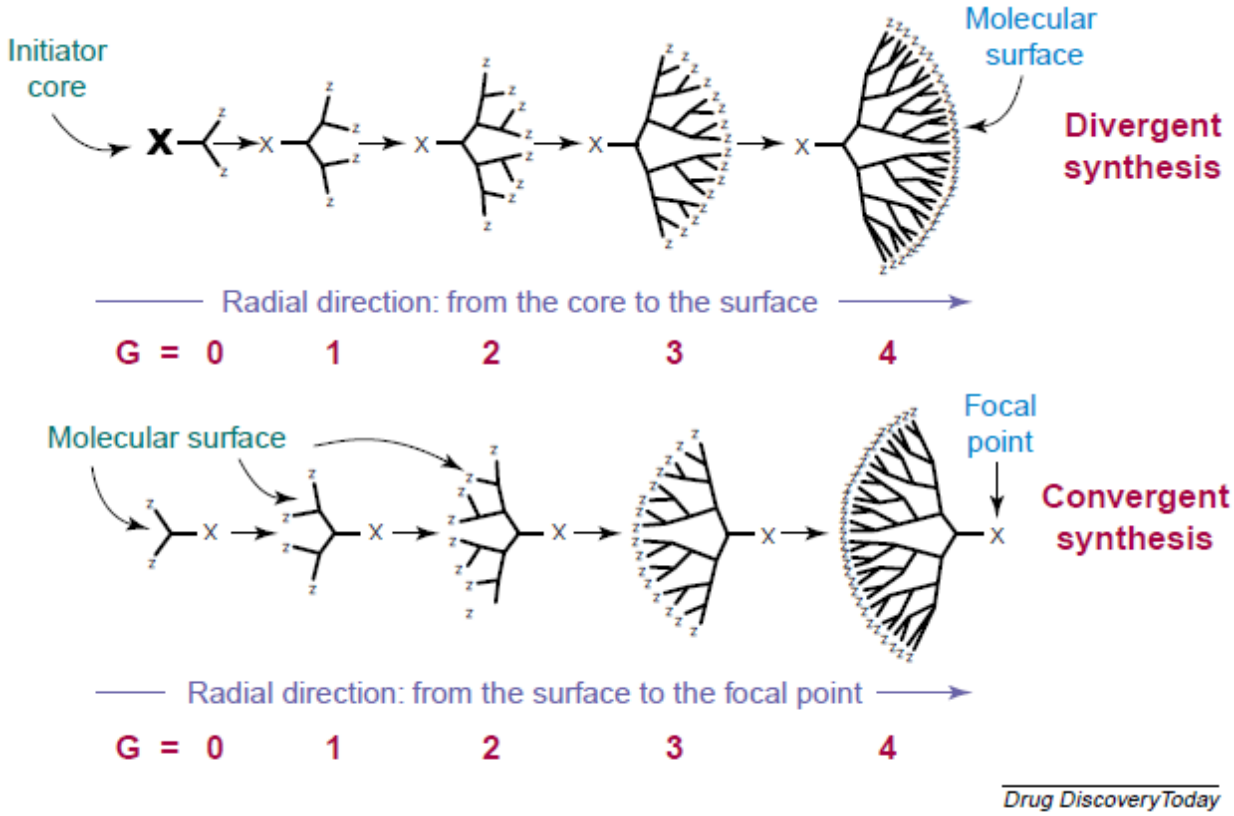

Figure: Two principle synthetic methods for constructing dendritic macromolecules (Dendrons):

(a) The divergent method, in which the synthesis begins from a polyfunctional core and continues radially outwards by successive stepwise activation and condensation,

(b) The convergent method in which the synthesis begins at what will be the periphery of the final macromolecule and proceeds inwards.

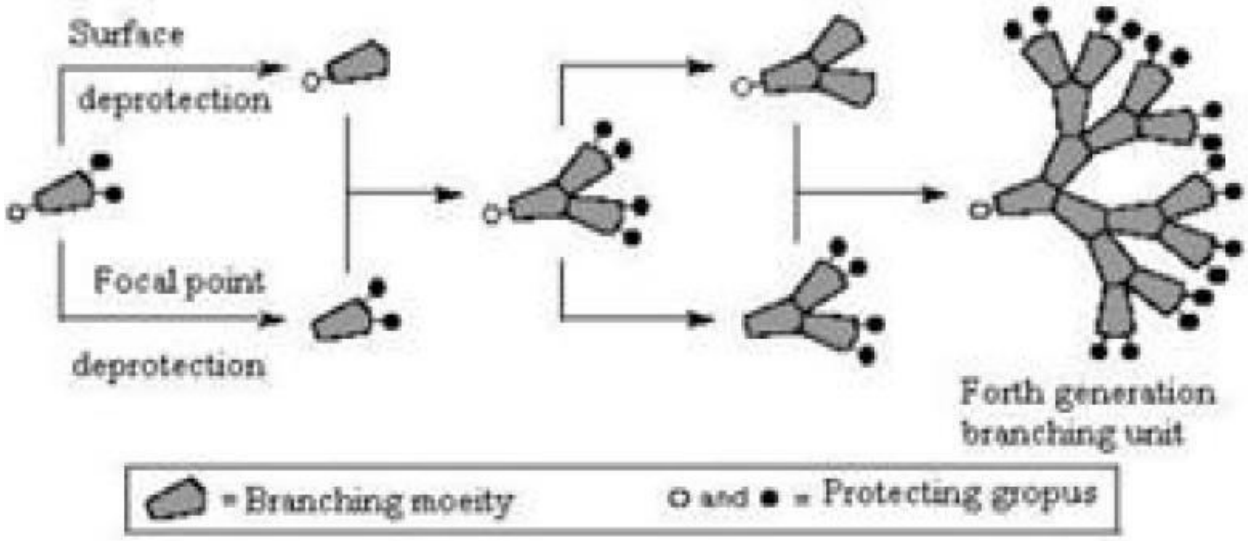

Figure: Double Exponential and Mixed Growth

(2) Accelerated Approach:

The divergent and convergent methods are largely used to synthesize various Dendrimers successfully, but both are suffering from common problem of multistep and laborious procedures. So they are time consuming processes, and overall low yield makes the macromolecules more expensive. Recently thus accelerated approaches are being used for the synthesis of Dendrimers. These are Double Exponential and Hyper core techniques. The common feature of both is to reduce the number of steps for the synthesis of Dendrimer drastically. This greatly accelerates the synthetic process and thereby decreases the work load and ultimately the cost of the polymer.

a) Hyper core and Branched monomer:

The approach involves the pre-assembly of oligomers, which can be then be linked together to offer the desired Dendrimer by a few steps with overall good yield. This approach is more like a convergent approach with less number of steps requirement for the generation of Dendrimers.

b) **Double exponential & Mixed 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. These two products are reacted together to give an orthogonally protected trimmers, 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.

APPPLICATIONS OF DENDRIMERS

Dendrimer possess its unique structural features like nanoscopic size, spheroidal surface, high branching, cavernous interior, etc. and exciting properties, like low viscosity, high solubility, high reactivity, in combination with the high functionalities of the dendritic polymers suggested that they have wide number of potential applications in different fields. These included medicinal and diagnosis application, gene therapy and chemical sensors, drug delivery system, adhesive and coatings, light harvesting material, catalyst, electronic applications, separating agents, and many more.

1. Dendrimers in biomedical field

   The dendritic polymer has advantage in biomedical applications. These dendritic polymers are analogous to protein, enzymes and viruses and easily functionalized. Dendrimers and other molecules can either be attached to periphery or can be encapsulated in their interior voids. The dendrimer should possess certain qualities for its utility as biological agents. The dendrimer should be nontoxic, non-immunogenic, bio permeable, able to target specific structure. Due to specific synthesis, Polyamidoamine (PAMAM) dendrimers possess the interesting properties, which distinguish it from classical linear polymers and are the most studied starburst macromolecule. PAMAM dendrimers can also be used to target tumour cells. Targeting groups can be conjugated to the host dendrimers surface 20 to allow the imaging agent to bond selectively to specific site such as receptors on tumour cell to improve detection. Cisplatin was complexed to the surface groups of a carboxylate-terminated PAMAM dendrimer which led to a tenfold increase in the solubility of cisplatin compared to the free drug 40. It was also found that the use of lower molecular weight dendrimers with denser interiors and ellipsoidal, flattered or elongated shaped may result in improved dendritic MRI contrast agents.

2. Dendrimer as magnetic resonance imaging contrast agents Dendrimer based metal chelates act as a magnetic resonance imaging contrast agent. Dendrimers are highly suited and used as image

contrast media because of their properties. Many tests carried on dendrimers have shown that dendrimers are stronger contrast agent than conventional ones. They can improve visualisation of vascular structure in magnetic resonance angiography (MRA) of the body. Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged enhancement with a half-life of 200 min compared to 24 min for monovalent gadolinium agent. This prolonged enhancement time is extremely useful for 3D time-of-flight MR angiography. In the recent study, it was found that the molecular size of a dendrimer-based MRI agent altered the route of excretion. Contrast agents having molecular weight less than 60 kDa were excreted through kidney being potentially suitable as functional renal contrast agents. Larger sized and hydrophilic contrast agents were found better for use as blood pool contrast agent. Larger hydrophilic agents were useful for lymphatic imaging. Finally, these dendrimer based MRI agents were recognised by the pharmaceutical industry which results in various commercial developments.

3. Dendrimers in Antitumor Therapy

Dendrimers molecule has found use as diagnostic reagent for tumour imaging by magnetic resonance imaging and as contrast agent; by varying the size and hydrophilicity and by combining with tumour targeting antibodies, these compounds can be used for a range of specific imaging purpose The drug used should be non-toxic, under nonirradiative condition, thus acting as prodrug when not irradiated. Dendrimers containing photosensitises named 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for photodynamic therapy (PDT) of tumorigenic keratinocytes . The administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue were involved in cancer treatment. Also, glycodendrimer constitute an important class of therapeutic molecules. The dendrimers were investigated with the purpose of producing a drug that would interact with carcinoma derived Tantigen- binding receptors to interfere with carcinoma growth. This type of Glycodendrimer reacted in a generation dependent way with monoclonal antibodies against the T-antigen with higher generation having higher affinities. The therapeutic uses of dendrimers may be within the cancer field where numerous examples of targeting tumours for diagnostic purpose have been described and where it is possible to define a cancer specific cell surface component that can be targeted.

4 .Dendrimers as Gene Transfer Reagents

Gene transfection is a direct approach where DNA is coupled to a nanoparticle of inert solid, which is then directly targeted to the cell nucleus. As transfection, if eukaryotic cells is a methodology for effective changes in the genetic material of cells. It has become much valuable tool in molecular biology for studying mutations and regulation processes of genes or inducing over expression of desired proteins. The ideal vector for transfection should be apart from high efficiency, non-immunogenic, non-toxic, either bio-degradable or excretable and has long blood circulation time. The use of dendrimers for transfection was first reported by the group of Szoka and Baker. PAMAM dendrimers were the first found to be useful for transfection. The company named Quiagen developed a commercial transfection system based on PAMAM dendrimers followed by the work of Szoda et al and Baker et al. Dendrimers are actively under investigation for the delivery of DNA and small organic molecule drugs, especially for cancer therapy. 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. It was also known that, the dendrimers of high structural flexibility and partially degraded high generation dendrimers are better suited for certain gene delivery operations. The delivery of therapeutic nucleic acids, normally in the form of plasmids, but increasingly also as smaller oligomers remains one of the major obstacles currently hampering the further exploitation of genetic therapies. The suitability of any gene delivery system will always have to be matched with the clinical situation, the specific disease and chosen therapeutic strategy. Furthermore, a series of amphiphilic dendrimers based on the rigid diphenylethyne core was synthesized and their activities as transfection agent were described. These dendrimers show high transfection activity, variety of substitution patterns, but the hydrophobic parameters influenced the DNA binding and transport more strongly than predicted, exhibits lower toxicity and an unusual serum effect. These dendrimers do not show a minimum size limitation for transfection. However, an optimum molecular weight greater than 116 kDa was found for PAMAM dendrimers which gave an optimum activity. In one of the study, dendritic amidoamine side chains of different generations were covalently attached to the chitosan which was chosen to combine the biological activities of chitosan in gene delivery, antibacterial activity and wound healing activity with the delivery benefits found for dendrimers .

5. Dendrimers in targeted drug delivery

Targeted drug delivery is a process of introducing medicine to a patient in a manner that increases the concentration of medication in particular part of body. A certain amount of therapeutic agent is delivered for a prolonged period of time to the targeted diseased area within the body, which helps to maintain the required plasma and tissue drug level in the body. Dendrimers have multifunctionality and high potential for drug delivery applications as they possess high density and wide variety of functional groups on its surface. It's well defined molecular structure, segmental spherical construction of dendrimers offers an interesting architecture for dendrimers. If one of these segments is attached with active drug molecule, the other can be highlighted as targeting group. Due to this double functional group, the plasma level of the drugs will stay at desired level for longer time period and increase its Pharmaceutical efficiency. Generally, the therapeutic efficiency of drug is diminished due to low bioavailability, insolubility, toxicity and the decomposition of drug under biological circumstances. Using Dendrimers containing targeting moieties onto conjugated drug molecule, the above shortcomings can be overcome.

6. Dendrimers in drug delivery

Drug molecule can be loaded in the interior and also to the surface of dendrimers. Encapsulation of the well-known anticancer drug cisplatin within PAMAM dendrimers gave conjugates which can slow down release and higher accumulation in solid tumours and it has low toxicity than free cisplatin. The encapsulation of silver salts within PAMAM dendrimers produces conjugates that can exhibit slow silver release rates along with antimicrobial activities against different gram positive bacteria . Dendrimers are highly soluble and compatible, due to which, solubility of drug in body can be increased. As dendrimers is water soluble and capable of binding and solubilising acidic hydrophobic molecules with antifungal and antibacterial properties. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation.Therapeutic agents can be attached to a dendrimer to direct the delivery. For example, dendrimers in boron neutron capture therapy (BNCT) Dendrimers .

7. Dendrimers in transdermal drug delivery

Transdermal drug delivery has come into existence long back. To improve the effectiveness of the drug transdermal drug delivery system was emerged. Drug delivery through skin to achieve a systematic effect of drug is known as transdermal drug delivery. Transdermal delivery provides controlled, constant administration

of the drug which extends the activity of drug having short halflife through the reservoir of drug present in the delivery system and its controlled release characteristics. The drug which is to be delivered should have low melting point, should be potent, having short half-life and non- irritating. PAMAM dendrimer complex with Non-Steroidal Anti-inflammatory Drugs (e.g. Ketoprofen, Diflunisal) which are very effective in treatment of acute and chronic rheumatoid and osteoarthritis, could be improving the drug permeation through the skin as penetration enhancers. The model drugs Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies.

8. Dendrimers in oral drug delivery

Oral drug delivery is the most popular and has received more attention in the pharmaceutical field because of ease of production, low cost, convenience of ease of administration and flexibility in designing of dosage. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and the patient, the length of the therapy and properties of the drug. The controlled release system for the oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. One important advantage of oral drug delivery is less fluctuating plasma drug level is maintained with controlled drug delivery systems, because the drug is slowly released from the dosage continuously and maintains the constant blood level. Along with the merits there are some demerits of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes. D'Emanuele and his research group investigated effect of dendrimer generation and conjugation on the cytotoxicity, permeation and transport mechanism of PAMAM dendrimer. As the concentration and generation increased, the increase in cytotoxicity and permeation of dendrimers resulted. While reduction in cytotoxicity was observed by conjugation with lauryl chloride.

9. Dendrimers in ocular drug delivery:

The topical application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. An ideal ocular drugdelivery system should be non-irritating, biocompatible, sterile, isotonic and biodegradable. The recent problems for ocular drug delivery focus on increasing the residence time of pilocarpine in the eye was overcome by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface modified dendrimers were predicted to enhance pilocarpine bioavailability.

10.Dendrimers in pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery also 50. In one of the studies, by measuring plasma anti-factor Xa activity using PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin, and by observing prevention efficacy of deep vein thrombosis in a rodent model, it was observed that G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40% while G2.5 PAMAM half generation dendrimers containing negatively charged carboxylic groups had no effect. So the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery.

11. Dendrimers used for enhancing the solubility

PAMAM dendrimers are expected to have potential applications in enhancing the solubility for drug delivery systems. Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micelle nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour. Dendrimers that are soluble in water are capable of binding and solubilising small acidic hydrophobic molecule with antifungal or antibacterial activities. Dendrimer possess unimolecular micelle and do not possess a critical micelle concentration. These characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure. Dendrimer based carriers' offers the opportunity to enhance the oral bioavailability of problematic drugs. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

12. Dendrimers for additives, printing inks and paints

Dendrimers can be used in toners material with additives which require less material than their liquid counterparts. Patented a dry toner compound dendrimers as charge enhancing species in the form of an additive. Using additives in printing inks, dendritic polymers ensure uniform adhesion of ink to polar and non-polar foils. Here, first the hyper branched compounds attach themselves to the pigment particles and there are still large numbers of functional groups remaining to give adhesion to the surface of the foils. Dendritic polymers used in polyurethane paints impart surface hardness, scratch resistance, chemical resistance, light fastness, weathering resistance as well as high gloss, because of which they are used in furniture and automotive industries. Use of Dendrimer additives in the composition of the invention is effective for altering the surface characterization of

thermo plastic resin after moulding. One of example for this is polycarbonates, which are widely used as an engineering thermoplastic for providing a unique combination of toughness, stiffness, high softening temperature and processibility.

13. Dendrimers in light harvesting material

A significant research has been of interest for designing molecules with controlled motion of charges. The use of Dendrimers is because of its multiple functionality and structural features. Moving from the periphery to the core, the functional groups decreases; which render dendrimers in light harvesting. Most of the literature report shows direction towards energy funnelling from the chromophore in the periphery to another chromophore at the core. A study on π-conjugated dendrimers family based on truxene and thienylethynylene were synthesised. These synthesised dendrimers show intrinsic energy gradient from periphery to the core along with broad absorption in the UV-vis range and proficient energy transfer to the lower energy centre. Hence, they are highly potential as light harvesting materials.

14. Dendrimers as Catalyst

Dendritic polymers have been used in large amount as catalyst. There are two major reasons for the advantage of using dendritic polymers. One of the reasons is possibility of creating a large dendrimer with many active sites. These types of catalyst are an intermediate between heterogeneous and homogeneous catalyst which can be separated easily by filtration. The second important reason is, there is possibility of encapsulating a single catalytic site whose activities can be enhanced by dendritic superstructure, Dendrimers have multifunctional surface with active catalytic site. Insoluble materials can be encapsulated such as metals, and transport them into a solvent in interior of dendrimer. Cooper and co-workers synthesized fluorinated dendrimers which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from water into liquid CO_2.

15. Dendrimers as Biomimics Dendrimers

Having their well-defined macromolecular dimensions and compartmentalised structure are ideal mimics for a wide variety of biomolecules. The commercially available dendrimers provide possibility to create micro environments. PAMAM dendrimers with their network consisting of numerous mixed tertiary amines. Dendrimers have ability to expose the multivalent surface for increased binding of biomolecules. Also, dendrimers have ability to create a micro environment inside the dendrimer, which makes artificial catalytic

sites or cavities possessing different properties for construction of enzyme mimics. Dendrimer molecules are characterized by zones of different density, depending upon the rigidity or the conformational mobility of their scaffold; they combine dense and less dense areas. They are flexible and have cavities to accommodate solvent to act as host compounds for guest substance. By using dendrimers more favourable qualities compared to naturally occurring proteins can be obtained. More densely packed structure compared to the natural proteins, for example certain peptide based dendrimer system show a significant increased resistance towards proteases. The dendrimer is also used as a building block to mimic a non-globular collagen structure, showing that dendrimers, although being mostly globular shaped, may be used as mimics of non-globular structures. Dendrimers may also mimic numerous protein –based receptors utilised in nature for specific biological recognition. Glycomometics are synthesized analogous carbohydrate whose structure has been simplified and modified, and is an active ingredient, which can be used for treatment of chronic inflammatory ailment such as rheumatism,dermatitisand soriasis. (According to Diederich et al) Dendritic porphyrin-metal complexes consist of flexible dendritic poly (ether amide) units 58. Study of first and second generations of this dendrimer revealed that the reduction potential is shifted towards positive values, than sufficient shielding is obtained.

16. Dendrimers as a separating agent

A study of variety of compounds synthesized to determine suitability for enhancing boron rejection by reverse osmosis and nanofilteration membrane to separate born from sea water has been developed. For separation, compound must have amphiphile chemical structure and form micelle in aqueous solution. As a new compound dendrimers with a high density of functional moiety, is able to form micelle structure which can be easily separated and recovered by ultra-filtration membrane. These micelles provide high functional density at the surface of the particle, high surface area and ease of separation for isolation and regeneration of the compound. It was found that unmodified commercial dendrimeric compounds containing amine and hydroxyl groups are generally more effective for boron absorption. Polyamidoamine (PAMAM) dendrimers are used as chelating agents for the removal of certain metal ions from waste water and from contaminated soil.Other modified chelating PAMAM and poly (propyleneimine) dendrimer are also reported to be good ligands for a various hard metal cations, or can be described as “nanosponges” for the removal of Polycyclic aromatic hydrocarbons and other particles .

CONCLUSION

The dendritic polymers are considered as the 21st century's highly branched novel and useful macromolecules. 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. The chemical modification of the dendritic polymers resulted in a wide range of variation in properties, hence their application. In order to realize their full potential, the simple methodology for synthesis need to be developed which allows faster and mass cycle synthesis to a level of an industrial acceptance. As the number of available dendritic polymers expands, their potential applications are also explored. However, to get the maximum benefits of the novel class macromolecules, a research by collaboration is very much essential. Finally it is one of the youngest and exciting fields of polymers researches where all branches of science can take part and hence, deserves more intensive attention.

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