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Review Article

Dendrimer: A Novel System in Pharmaceuticals

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ABSTRACT

Dendrimers are a new class of synthetic polymers which have a tree or star shape like structure, with a central core, interior branches and terminal groups which embellish the surface. It can be synthesized by a repetitive step-growth polymerization process. They are highly branched and monodisperse macromolecules. The structure of dendrimers mainly affected to its physical and chemical properties; so, it is widely used in biomedical, pharmaceuticals and industrial applications. In Drug delivery system, dendrimer plays major roles in ophthalmic, topical, transdermal, targeted drug delivery since last decade. Recent progress has been made in the application of biocompatible dendrimers to cancer and AIDS treatment, including their use as delivery systems for potent anticancer drugs such as cisplatin and doxorubicin, as well as agents for both boron neutrons capture therapy and photodynamic therapy. It is alsoinhibiting the entry of HIV and herpes simplex virus (HSV). This review articles giveswhole idea about various dendrimers, its type and its properties. Also it considers brief idea about various dendrimers used in various areas of research, treatment and diagnosis.

Keywords: Dendrimer, PAMAM, reticuloendothelial system

INTRODUCTION

Dendrimers are synthetic macromolecules which can be differentiated from linear polymers by its unique characteristics. It has 'tree-like' structure which makes dendrimers distinctive from other polymers. Typical structure of dendrimer consist of a core molecule C, surface molecules S, interior branching, and multiple layers in which first generation G1, second generation G2 as shown in Fig. 1. In 1978, Vogtle produced first dendrimer by synthesis procedure known as a "cascade" synthesis. Interior void space and surface functional groups in dendrimers are well-suited for use as carrier molecules in drug delivery.[1,2] The results of Tomalia's group efforts on the first dendritic structures of polyamidoamine (PAMAM)[3] notified that the "divergent" synthesis technique provided rich functionality area on the outer surface. In July 2003 the FDA allowed the First clinical trials of a dendrimer based pharmaceutical Vivagel™ which is used as Vaginal Gel for preventing HIV. Nowadays so many products like Stratus® CS (Cardiac Marker)[4], Alert Ticket™ (Anthrax Detection)[4] and SuperFect™ (Gene Transfection)[5] easily accessible in marketin dendrimer form.

DENDRIMER: A POLYMERIC MACROMOLECULE

The word "dendrimer" originated from two words, the Greek word dendron, meaning tree, and meros, meaning part.[4]Dendrimers are synthesized by a repetitive step-growth polymerization process. For example, diaminobutane core containing Starburst®

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(Starpharma, Melbourne, Australia) (PAMAM) dendrimers are synthesized with alternating reaction with acrylic acid methyl ester and ethylenediamine.[3] When a dendrimer reaches generation greater than about four during the step-wise synthetic process (depending on its chemistry), it undergoes a significant conformational change and predicts a densely packed globular shape.[6]

Intrinsic viscosity is another important characteristic that distinguishes dendrimers from more conventional polymers.[7] In contrast, dendrimers exhibit a bell-shaped viscosity curve, where viscosity increases at lower generation numbers, reaching a maximum, which corresponds to a change in the conformation and beyond which the intrinsic viscosity decreases at its higher molecular weight (Fig. 2).[8] This feature is very useful in formulation science, as this high molecular weight, higher-generation dendrimers do not tend to be highly viscous therefore handling and formulation is easy compare to other linear polymers. Another one of the important desirability of using dendrimers for delivery systems comes from their property of being highly soluble in a large number of organic solvents so, they are highly suitable in drug delivery vehicle. Also dendrimers are being developed as in vitro as well as in vivo diagnostics, as gene transfection agents.[9]

A single dendrimer is capable of making many binding contacts with multiple copies of a cellular target. This multiplicity of binding is known as multivalency or polyvalency.[10] It is increasingly being recognised to overcome intrinsically weak monovalent interactions, and of generating drugs with totally new activities, modes of action and pharmacokinetic profile. Also a half-life of various drugs which are used for the drug delivery system can be enhanced with the use of different types of dendrimers. Unmodified drug doxorubicin & methotrexate both have 0.5 hr. Half-life while in dendrimer form their half-life is extended up to 34 hr. and >50 hr. respectively.[11]Furthermore insulin-dendrimer shows prolonged suppression of blood glucose in vivo.[11]Although widely researched for more than two decades, only one clinical study is underway using dendrimers as microbicides.[12]

Advantages of Dendrimers

Dendrimers offers various advantages over linear polymers:

i. Dendrimers have nanoscopic particle size range from 1 to 100 nm, which makes dendrimers less susceptible for reticuloendothelial system (RES) uptake.

ii. Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectively than any other small molecules.

iii. Multiple functional groups which are present at outer surface of the dendrimers, which can be used to attach vector devices for targeting to particular site in the body.

iv. Dendrimers can be modified as stimuli responsive to release drug.

v. They have lower poly dispersity 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; so, most of the space remains hollow towards core. This region can be utilized for drug entrapment.

vi. 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. [13-15]

Mechanisms of Drug Loading onto Dendrimer Carriers

The internal cavity of an appropriately designed dendritic structure could be used for the entrapment of drugs with the possibility of

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successive controlled release. Studies by several research groups[16]have shown that the interior of a dendrimer is capable of encapsulating guest molecules. The first strategy for the entrapment of guest molecules in dendrimers is physical encapsulation. It was reported that guest molecules such as Rose Bengal can be physically entrapped in the internal cavity of high generation poly (propylene imine) dendrimers when an amino acid derivative is used to lid each end group of the dendrimer (the 'dendritic box').[16]

The second strategy for the encapsulation of guest molecules in dendrimers is based on multiple noncovalent chemical interactions, such as hydrogen bonding, between guest molecules and the dendritic arrangement. Newkomeet al. reported a dendritic host containing multiple hydrogen bonding sites at its core; it was evaluated by 1H NMR titration.[17]

The third, and easily implemented, strategy for the encapsulation of guest molecules in dendrimers makes use of hydrophobic interactions. Newkomeet al prepared dendritic macromolecules with a hydrophobic interior and hydrophilic chain ends (Fig. 3) [17]

PROPERTIES OF DENDRIMER

Various significant properties for dendrimers are there which makes dendrimers more effective and useful in drug encapsulation.

Monodispersity:

Dendrimers are the class of dendritic polymers that can be assemble with a well-defined molecular structure, i.e. being mono-disperse, unlike to linear polymers. Monodispersity offers researchers the opportunity to work with a tool for well-defined scalable size for different types of research work.

Nanoscale size and shape:

These fundamental properties have in actual fact lead to their commercial use for gene therapy, immunodiagnostics and variety of other biological applications like drug delivery, therapeutics and diagnostics.

Polyvalency:

Polyvalency shows the outward arrangement 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. Vivagel™ a topical vaginal microbicide prevents infection by HIV and other sexually transmitted diseases during intercourse takes benefit of dendrimers polyvalent properties.[4]

Physicochemical properties of dendrimers

Dendrimers have some unique properties because of their spherical shape and the presence of internal cavities. The most significant one is the possibility to encapsulate guest molecules in the macromolecule interior. Also the use of dendrimers as protein mimics has been optimistic scientists to investigate the physicochemical properties of dendrimers in comparison to proteins shows that dendrimers, similar to protein.[18]

Biocompatibility of dendrimers

In order to using of dendrimers as biological agents, they should be nontoxic, non-immunogenic, able to cross bio-barriers (bio-permeable), able to stay in circulation for the time needed to have a clinical effect and also able to target to specific structures. The cytotoxicity of dendrimers has been chiefly evaluated in vitro; however, a few in vivo studies have been published.[19] Dendrimers with positively charged surface groups is prone to subvert cell membranes and cause cell lysis. Comparative toxicity studies on anionic (carboxylate-terminated) and cationic (amino-terminated) PAMAM dendrimers using Caco-2 cells have shown significantly lesser cytotoxicity of the anionic compounds.[20] Furthermore, the cytotoxicity was found to be generation reliant with higher generation dendrimers are being most toxic.[21] The degree of substitution as well as the type of amine functionality is also very

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important. Dendrimer with primary amines is being more toxic than secondary or tertiary amines. [22]

Immunogenicity

Immunogenicity is one of the essential biological properties of the dendrimers. As per research of unmodified amino terminated PAMAM dendrimers are showing no or only weak immunogenicity of the G3–G7. PAMAM dendrimers with polyethylene glycol (PEG) chains decrease immunogenicity and gives longer lifetime in the blood stream in comparison to unmodified dendrimers. [23]

TYPE OF DENDRIMERS:

Radially Layered Poly (Amidoamine Organosilicon) Dendrimers (Pamamos): Dr.Petar Dvomic et al. find out first commercial silicon containing dendrimers.[24] It consists of nucleophilic polyamidoamine (PAMAM) interiors which are hydrophilic in nature and also contain organosilicon (OS) exteriors which are hydrophobic in nature. Because of its excellent capacity to form complex it is widly used in nanolithography, photonics, and electronics and also used as chemical catalysis.[24] Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method. In high generation it's looking like star shaped. They are available in market up to G11 generation with different types of core. Barbara et al. mention Physiochemical Properties of PAMAM-NH2 Dendrimers (G0-G11) with EDA Core (Table 1). [27]

These distinctive characteristics of PAMAM dendrimers allow for direct conjugation and physical entrapment of anticancer drug molecules to widen dendrimers-based drug delivery systems.[25]

Table 1: Physiochemical Properties of PAMAM-NH2 Dendrimers (G0-G11) with EDA Core [27]

Generation	Molecular weight (Daltons)	Diameter (A)	Surface groups (-NH2)	Radius of Gyration (A)
G0	517	15	4	4.93
G1	1430	22	8	7.46
G2	3256	29	16	9.17
G3	6909	36	32	11.2
G4	14215	45	64	14.5
G5	28 826	54	128	18.3
G6	58048	67	256	22.4
G7	116 493	81	512	29.1
G8	233383	97	1024	36.4
G9	467162	114	2048	46.0
G10	934720	135	4096	55.2
G11	1869 780	167	8192	68.3

Poly (Propylene Imine) Dendrimers (PPI)

These types of dendrimers are available up to G5 generation in present market. They have tertiary tripropylene amine as an interior portion and also have poly-alkyl amines present as end groups of dendrimers. PPI dendrimers are available in market in form of Astramol.[26-27]

Chiral Dendrimers

Andreas Ritzen et al Synthesise chiral dendrimer based on polyfunctional amino acids. Mainly use of these chiral dendrimers for enantiomeric resolution and it's also use as catalysts in asymmetric synthesis.[28]

Liquid Crystalline Dendrimers

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Liquid crystalline dendrimers contains mesomeric group in its highly branched structure. They contain high amount of oligomer or polymer in its structuree.gCarbosilane dendrimer.[29]

Tecto Dendrimer

With various significant of tecto dendrimers they are widely used in diagnosis of disease state drug delivery, identified location for outcome therapy. Also perform varied function by identified different types of diseased cell.[30]

Hybrid Dendrimers

They are hybrid combination form of dendritic and linear polymers. They are produced by complete monofunctionalization of peripheral amine of zero generation present in polyethyleneimine dendrimer. Hybrid dendrimers produced diverse lamellar, columnar and cubic type lattices which are not available from other dendritic structures.[31]

Peptide dendrimers

Dendrimers having peptides on the surface of the conventional dendrimer framework and dendrimers incorporating amino acids as branching or core units are both defined as 'peptide dendrimers'. These dendrimers can be used as drug delivery, contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and also insero diagnosis.[32]

Multilingual Dendrimers

In multilingual dendrimers specific functional group are present in multiple amounts on the surface of dendrimer.[4, 30]

Micellar Dendrimers

They are unimolecular in nature. Hyper branched polyphenylenes micelles are used which are highly water soluble in nature.[30]

APPLICATIONS:

Dendrimers in Drug Delivery

Polymer-based drug delivery systems are designed to improve the pharmacokinetics and bio-distribution of a drug and also provide controlled release kinetics to the proposed target. The ideal dendrimer carrier should exhibit high aqueous solubility and drug loading capacity, biodegradability, low toxicity, specificity, complimentary retention and bio-distribution characteristics, and appropriate bioavailability. In dendrimer-based drug delivery, a drug is either non-covalently encapsulated in the nucleus of the dendrimer or covalently conjugated to form macromolecular prodrugs. Various Drugs studied (Table 2) using different dendrimers and routes of administration.[33]

Table-2 Various Drugs studied using diff. dendrimers & routes of administration [36]

Sr. No.	Routes of administration	Dendrimer	Drug
1	IV	PEGylated PAMAM dendrimer Galactose-coated PPI dendrimer	5-Fluorouracil Primaquine phosphate
2	IM	Polyester dendrimer PEGylated peptide dendrimer	Doxorubicin Artemether
3	Transdermal	PAMAM dendrimers PAMAM dendrimers	Tamsulosin Indomethacin
4	Ophthalmic	PAMAM dendrimers PAMAM dendrimers	Tropicamide Pilocarpine
5	Oral	PAMAM dendrimers	5-Fluorouracil

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Dendrimers as Ophthalmic Vehicles

Some current research efforts in dendrimers for ocular drug delivery include PAMAM dendrimers that were studied by Vandamme and Brobeck as ophthalmic vehicles for controlled delivery of pilocarpine and tropicamide to the eye.[34] In albino rabbit model, the residence time of pilocarpine in the eye was improved by using dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were expected to enhance pilocarpine bioavailability.[34]

In another study, dendrimer end groups were conjugated with aminosaccharides and sulfated aminosaccharides to acquire anionic dendrimers with distinctive biological properties.[35]

Dendrimers in pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers improved the relative bioavailability of Enoxaparin by 40 %.[36]

Dendrimer in oral drug delivery

Oral drug delivery studies using the human colon adenocarcinoma cell line, Caco-2, have indicated that low-generation PAMAM dendrimers cross cell membranes, most probably through a combination of two processes, one is paracellular transport and another is adsorptive endocytosis. Remarkably, the P gp efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are capable to bypass the efflux transporter.[37] PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging it respectively. DNA assembled dendrimer conjugates may permit the combination of different drugs with different targeting and imaging agents so combinatorial therapeutics is easy to develop.[25]

Dendrimers for controlled release drug delivery

Control the rate of drug release from the inclusion complexes is to encapsulate them in a liposomal envelope forming modulatory liposomal controlled release systems (MLCRS).[38]

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers which had been customized with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construct involving PEG chains and PAMAM dendrimers was also used to deliver the anticancer drug 5-fluorouracil. Encapsulation of 5-fluorouracil is increased in the cytotoxicity and permeation of dendrimers in targeted cell.[39]

Topical and Transdermal Delivery:

Dendrimers have established recent applications in novel topical and transdermal delivery systems, providing benefits such as improved drug solubilisation, drug-polymer conjugates (pro-drugs) and also controlled release.[40] For ease of handling of highly concentrated dendrimer formulations for these applications viscosity-generation-number property is generally used. Dendrimers have been used as transdermal and topical drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs), antiviral, antimicrobial, anticancer, or antihypertensive drugs. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAIDs are ketoprofen and diflunisal.[40] Also transport of indomethacin through intact skin was enhanced in vitro and in vivo has been studied earlier.[41]The bioavailability of indomethacin was increased by using G4-PAMAM dendrimers with terminal amino groups. Molecular diffusion through intact skin is associated to the molecular weight of the permeate molecule. These dendrimers

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generally have low diffusion coefficients because of their high diffusion rates. Diffusion through skin is more favourable for those molecules that have solubility in lipids as well as in water. Different generation (G2-G4) PAMAM dendrimers have the potential to considerably enhance the solubility of NSAIDs.[42]

DENDRIMERS IN THERAPEUTICS

Dendrimers in Gene Therapy

Effective non-viral vectors for gene delivery are actively sought because dendrimers are used to improved immunogenicity. It protects DNA from enzymatic degradation and to help deliver it into the cell because they form compact polycations under certain physiological conditions. PAMAM dendrimers, poly (propylene imine) dendrimers and partially hydrolyzed PAMAM dendrimers have been used as DNA delivery systems.[43-45]By scanning force microscopy data it is observed that DNA wraps around the dendronized polymers.[46] In recent reports, electroporation and addition of β-cyclodextrin were combined with DNA–dendrimer systems. Electroporation caused significant enhanced in gene expression[47] and addition of β-cyclodextrin caused development of smaller and more monodisperse particles.[48]

PAMAM dendrimers functionalized with α-cyclodextrin proved gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and α-cyclodextrin.[49] Poly(ethylene glycol) functionalization of G(5)-PAMAM dendrimers formed a 20-fold increase in transfection efficiency using plasmid DNA coding for a reporter protein β-galactosidase relative to partially degraded PAMAM dendrimers.[50] Some of the polycation–DNA complexes were less toxic than lipid–DNA systems. A degraded PAMAM dendrimer carrier was one of the more competent polycations for DNA delivery, but its cytotoxicity was also important. [43]

Dendrimers in cancer therapy

Poly (glycerol succinic acid) dendrimers (PGLSA) were considered as delivery vehicles for camptothecins, a group of naturally-derived hydrophobic compounds with anti-cancer activity. In a preliminary study reported by the Grinstaff group, G4-PGLSA dendrimers with hydroxyl (G4-PGLSA-OH) or carboxylate (G4-PGLSA-COONa) peripheral groups were used to encapsulate 10-hydroxycamptothecin (10-HCPT) for delivery to cancer cells.[44] This dendrimer can be used as a delivery vehicle for 10-HCPT and 7-butyl-10 aminocamptothecin (BACPT), a highly potent lipophilic camptothecin derivative. The release profile of 10-HCPT encapsulated G4-PGLSA-COONa showed full release of the drug within approximately 6 hr, suggesting that the delivery system may be best utilized by intratumoral injection.[46] The anti-cancer drugs doxorubicin and etoposide were encapsulation efficiency while the more lipophilic etoposide achieved a loading capacity of approximately 22% by weight.

Enhanced aqueous solubility of paclitaxel was achieved with poly(glycerol) dendrimer formulations, showing that a hydrophobic dendrimer core is not necessary for encapsulation and solubilisation of hydrophobic drugs.[48] Paclitaxel solubilities ranged from 80–128 μg/mL with increasing generations from G3–G5 of poly (glycerol), or three orders of magnitude higher than free paclitaxel.[48]

Melamine-based dendrimers were used to solubilize the anticancer drugs methotrexate and 6-mercaptopurine, as well as to reduce drug toxicity. Therapeutic agents are internalized within the interior core space or by micellar formation of the dendrimers.[49]

A major drawback to these delivery systems is a lack of controlled drug release kinetics, with most systems releasing their payload over the course of several hours. For this reason drug-encapsulated dendrimer systems may best be utilized via direct intratumoral injection.

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Dendrimer-Drug Conjugates

Dendrimer-drug conjugates usually consist of an antineoplastic agent covalently attached to the peripheral groups of the dendrimer. This method offers different advantages over drug-encapsulated systems. Multiple drug molecules can be attached to each dendrimer molecule and the release of these therapeutic molecules is partially controlled by the nature of the linkages. The Kannan group reported the synthesis of PAMAM-methotrexate conjugates obtained from the carboxylic acid or amine group in order to check the activity of mrthotrexte in human acute lymphoblastoidleukemia and Chinese hamster ovary cell line indicates the potential of dendrimer drug conjugates for the treatment of cancer cells.[50]

Paclitaxel was conjugated to PEG or G4-PAMAM to compare the anti-cancer activity of the drug delivered by a linear or dendritic carrier.[51] Doxorubicin-G4-PAMAM complexes have been encapsulated into liposomal formulations for potential local delivery to locations such as skin metastasis from breast cancer.[52]

It is clear that dendrimer-drug conjugates are highly capable of delivering a payload with sufficient bioavailability to achieve a therapeutic goal. The release of covalently linked drug is dependent upon the chemical linkage binding the agent to the carrier. Novel dendrimer structures are being synthesized to further explore finer control of release kinetics.

Dendrimers in photodynamic therapy

This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue. The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for Photodynemic therapy of tumorigenic keratinocytes.[53]

Dendrimers for boron neutron capture therapy

Boron neutron capture therapy (BNCT) refers to the radiation generated from the capture reaction of low-energy thermal neutrons by ^{10}B atoms. This radiation energy has been used successfully for the selective destruction of tissue. Dendrimers are a very fascinating compound for use as boron carriers due to their well-defined structure and multivalency. The first example of boron containing PAMAM dendrimer was synthesized.[54]

Dendrimer in HIV and HSV Infection

Dendrimer are useful to inhibiting the entry of HIV and herpes simplex virus (HSV) types 1 and 2. Dendrimer compound Vivagel™, inhibit the replication of HIV-1 (Strain IIIB) in a range of cells types with an EC50 of <1µg/mL [55] the compounds were non-toxic to the cells up to the highest concentration. Dendrimers are also effective in protecting primary foreskin fibroblast cells in vitro from the cytopathic effects of HSV-1 and inhibiting the early stages of viral replication. In mice intravaginal infection was extended to 30 minutes when given an intravaginal dose of a representative dendrimer – SPL2999 [56] Dendrimer SPL7013 which possessed both a high level and wide range of activity against HSV and HIV.[57]

Diagnostic application of Dendrimer

Dendrimers as molecular probes

Dendrimers are fascinating molecules to use as molecular probes because of their distinct morphology and unique characteristics. For example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular probe, because of their large surface area and high density of surface functionalities.[58]Silica nanoparticle-based molecular probes used for bimodal quantitative monitoring for enzymatic activity with simultaneous signal increases in 19F NMR and fluorescence.[59]

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Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools applicable to numerous diseases in medicine. To obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent.[60] Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Krause and co-workers synthesized a number of potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin.[61]Weir MG et al. also reported an in situ X-ray absorption-fine structure (XAFS) spectroscopic analysis of ~1.8 nm Pt dendrimer-encapsulated nanoparticles (DENs).[62]

Dendrimers as MRI contrast agents

A number of research groups have explored the use of dendrimers as a new class of high molecular weight MRI contrast agents. Wiener and co-workers developed a series of Gd(III)–DTPA-based PAMAM dendrimers.[63]To improve the pharmacokinetic properties of dendrimer contrast agent introduction of target specific moieties to the dendritic MRI contrast agents have been considered. Wiener et al. synthesized a folate conjugated Gd(III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.[64] Recently, the combined use of paramagnetic chelates and fluorescent groups conjugated to the surface of PAMAM dendrimers have facilitated dual-mode imaging of lymph nodes by both MR imaging and fluorescence microscopy.[65]

Detection of Molecules with Biological Importance:

Modified surfaces with nano-structured composites of Prussian Blue (PB) and Dendrimers represent some of the most promising approaches for the development of efficient and new materials for advanced electrochemical applications. As the PB interacts in supramolecular manner with PAMAM dendrimers in aqueous medium, across the hydrophobic zone of dendrimer, they form composites stables in solution with different generations of PAMAM.[66]

Dendrimers make the function of endoreceptors of PB forming composites of PB – PAMAM dendrimers, which can work as electro-catalysers to detect molecules with biological importance. The electrocatalysis is proportional with the increase of dendrimer generation, where the covalent modified electrodes are more sensible and selective than electrostically modified electrodes.[66]

A simple DNA biosensor based on the application of dendrimer is developed. This work shows that the dendrimer – DNA compatibility, which is being exploited in the field of gene delivery, can be applied in the development of.[67]

Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecularmicellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour.[68]

ChengYiyun et al worked on solubilization of non-steroidal anti-inflammatory drugs in the presence of polyamidoamine dendrimers and results showed that the solubility of NSAIDs in the PAMAM dendrimer solutions was approximately proportional to dendrimer concentration.[69]

DENDRIMER: IN MARKET

In July 2003 the FDA allowed the first clinical trials of a dendrimer based pharmaceutical: vivagel™ which is vaginal gel to prevent HIV.[70] Nowadays so many products like Stratus™CS

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used as cardiac marker prepared by Dade Behring,[71] Superfect™ used for gene transfection made by Qiagen[72] and Alert Ticket™ prepared by US Army Research Laboratory used for anthrax detection based on dendrimer accessible in market.[4] Most recently Starpharma announced pre-clinical results in its docetaxel (Taxotere) program demonstrating significant improvements in anticancer efficacy and the enhancement of solubility offering potential safety benefits of anticancer agent.[73]

The Swedish company perstorp sells dendrimer-like materials for a variety of applications, high performance varnish for boats being only one example. DSM, in the Netherlands, has a new type of dendritic-based material that promises to reduce the number of steps in the papermaking process, making it much more efficient and environmentally friendly. Some other dendrimer-based products that are in process of reaching commercial reality include Avidimers™ **(**Avidimer Therapeutics, Ann Arbor, MI) for cancer prevention and treatment and gadolinium-based MRI contrast agent.[34]Starpharma, in collaboration with its US-based wholly owned company Dendritic Nanotechnologies (Mount Pleasant, MI), recently announced the commercial launch of its Priostar™ dendrimer-based technology research product called the NanoJuice Transfection Kit in addition to the Starburst- and Priostar-based dendrimer family.[34]Because of the presence of large numbers of functional groups, these highly branched dendrimers are capable of binding to DNA. They will be useful for transfection of DNA into the variety of difficult-to-transfect cells.

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.

FIGURES: G1: Generation 1, G2: Generation 2, IC: Internal Cavity, C: Core

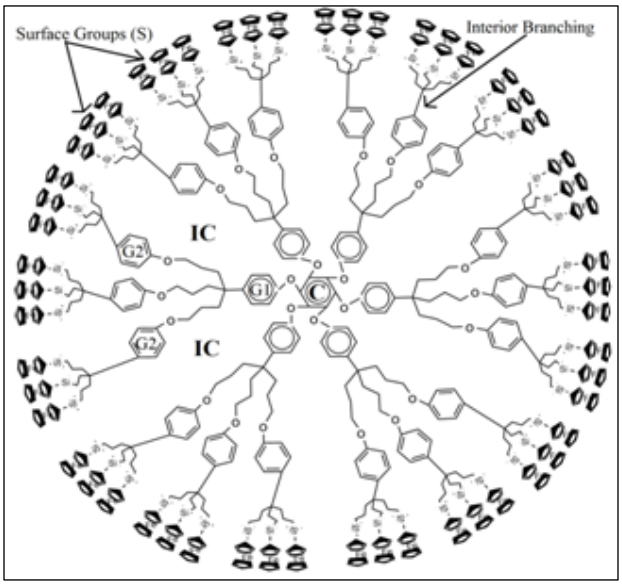

Fig.1 Structure of Dendrimer

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Fig. 2: Molecular weight vs. intrinsic viscosity

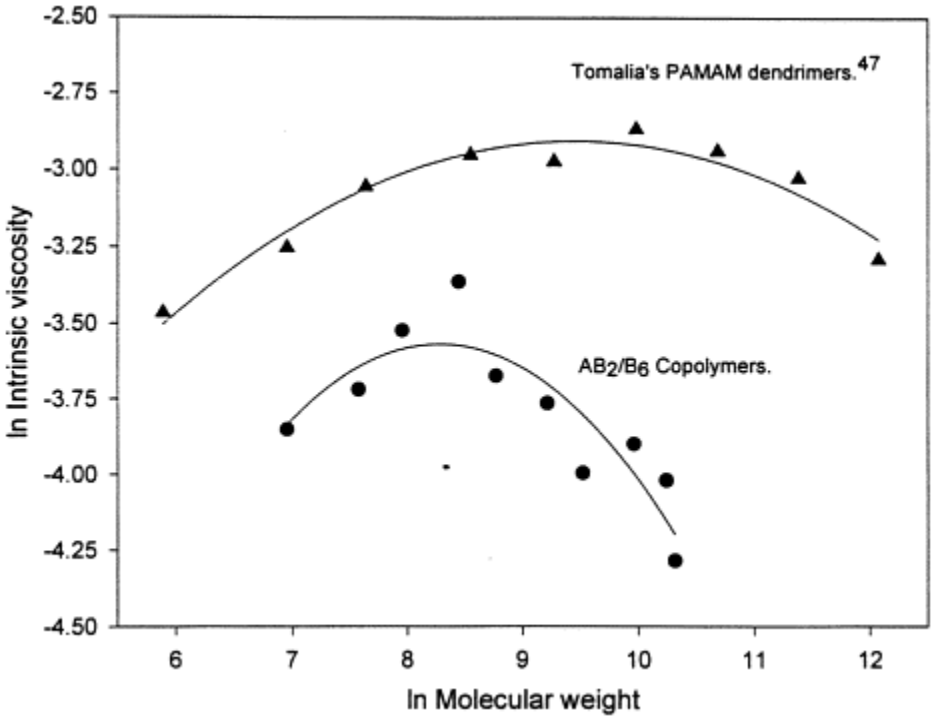
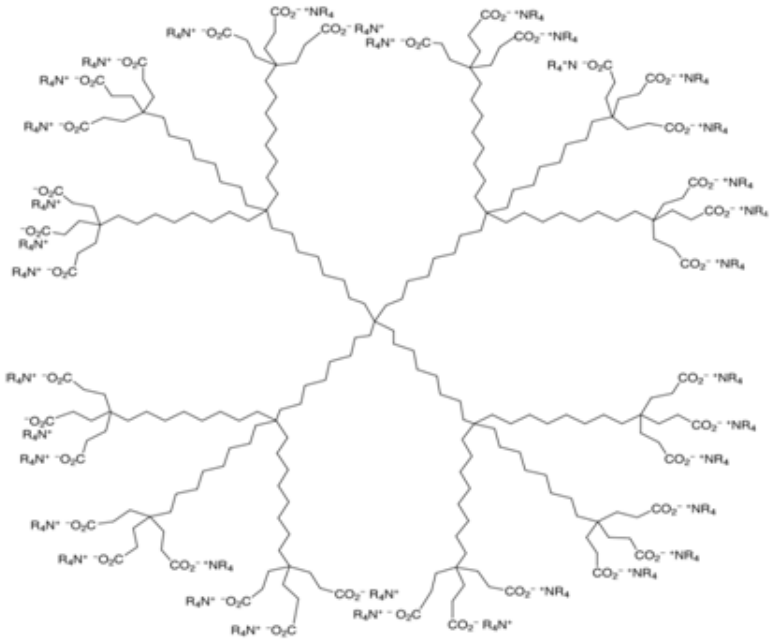


Fig. 3 Structure of the unimoleculardendritic micelles with hydrocarbon interior and carboxylate periphery prepared by Newkomeet al[18]



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