Dendrimer: a novel approach for drug delivery systems

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**ARTICLE INFO:**

**Article history:**
Received: 20 May 2016
Received in revised form: 15 June 2016
Accepted: 1 July 2016
Available online: 30 September 2016

**Keywords:**
Dendrimer,
Divergent growth,
Solubility enhancement,
Drug delivery

**ABSTRACT**

Dendrimers are hyper-branched macromolecules having tree like structure, consisting of a core molecule and alternating layers of monomers. So they can be synthesized by divergent and convergent growth methods. During synthesis, properties of dendrimers like dendrimer size, molecular mass, surface group can be controlled and configured to the desired need. Dendrimers have the ability to encapsulate and bind the guest molecule can be used for solubility enhancement, sustained release and various drug delivery applications. The reflections on biomedical and industrial applications of dendrimers given in this report clearly demonstrate the potential the class of polymer architecture and indeed substantiate the high hopes for the future of dendrimers.

**Introduction**

Dendrimers are generally described as a macromolecules, which is characterized by its highly branched 3D structure which gives a high degree of surface functionality and versatility. Polymer chemistry and technology have traditionally focus on linear polymers, which are used widely. Linear macro-molecules occasionally contain some smaller or longer branches. It has been recently found that the properties of highly branched macromolecules can differ drastically from conventional polymers. The structure of these materials has a greater impact on their applications. It was first discovered in early 1980’s by Donald Tomalia and co-workers, these hyper-branched molecules were called dendrimers. The term has been originated from ‘dendron’ which means a tree in Greek. At the same time, Newkome’s group reported synthesis of similar macromolecules of dendrimer they called them arborols from the Latin word ‘arbor’ also meaning a tree. [1, 2, 3] In July 2003, the FDA allowed the 1st clinical trials of a dendrimer based pharmaceutical VivagelTM which is used as Vaginal gel for preventing HIV. Nowadays many products like Stratus®CS(Cardiac Marker), Alert TicketTM (Anthrax Detection) and SuperFectTM (Gene Transfection) easily accessible in dendrimer form.[4]

**Properties of dendrimers**

Various remarkable properties for dendrimers which makes dendrimers more effective and useful in drug encapsulation.

**Monodispersity:** These are the class of dendritic polymers that can be assemble with a well-defined molecular structure that is being mono-disperse, unlike to linear polymers. Monodispersity favours researchers to work with a tool for well defined scalable size for various types of research work.

**Nanoscale size and shape:** These fundamental properties lead to commercial use for gene therapy, immune-diagnostics and variety of other biological applications like drug delivery, diagnostics and therapeutics.

**Polyvalency:** Polyvalency shows the outer arrangement of reactive groups on the exterior of dendrimer nanostructure. This creates more connections between surfaces and bulk material for applications such as adhesives, polymer cross-linking or surface coatings. VivageTM a topical vaginal microbicide prevents infection by HIV and other STD’s during intercourse gains benefit of dendrimers polyvalent properties.[4]

**Physicochemical properties of dendrimers:** Dendrimers have unique properties because of their spherical shape and presence of internal cavities. The most significant is the possibility to enclose guest molecules in the macromolecule.
interior. Also the use of dendrimers as protein resemblance has been optimistic for scientists to explore the physicochemical properties of dendrimers in collation to proteins shows that dendrimers, same as that of protein.[5] Biocompatibility of dendrimers: In order to use dendrimers as biological agents, they should be non-toxic, non-immunogenic, able to cross bio-barriers, able to stay in blood circulation for the time required to have a clinical effect and also able to target specific structures. The cytotoxicity of dendrimers has been mainly evaluated in-vitro; however, a few in-vivo studies have been published. Surface groups of dendrimers which are positively charged are vulnerable to destabilize cell membranes and cause cell lysis. Comparative toxicity studies on anionic (carboxylate-terminated) and cationic (aminoterminated) PAMAM dendrimers using Caco-2 cells have shown remarkable less cytotoxicity of the anionic compounds. Furthermore, the cytotoxicity resulted to be generation dependent with higher generation dendrimers are being most toxic. The degree of substitution as well as the type of amine functional group is also very important. Dendrimers with primary amines is relatively more toxic than secondary or tertiary amines.[4]

Immunogenicity: Immunogenicity is one of the crucial biological properties of the dendrimers. As per research, unmodified amino terminated PAMAM dendrimers are presenting no or only weak immunogenicity of the G3–G7. PAMAM dendrimers with polyethylene glycol chains decrease immunogenicity and offers longer lifetime in the blood stream in comparison to un-modified dendrimers.

Structure of dendrimers

Dendrimers are made from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that creates a spherical branching structure. As the process repeats, successive layers are adjoined, and the sphere can be expanded to the size needed by the investigator. The result is a spherical macromolecular structure whose size is in resemblance to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex.

Dendrimers consists of 3 distinguished architectural components [4, 5, 6]
(i) An initiator core.
(ii) Interior layers (generations) constitute of repeating units, basically attached to the interior core.
(iii) Exterior (terminal functional group) attached to the outermost interior generations, as shown above.

Components of dendrimers:[7- 9]

Fig:1 Structure of Dendrimer

Generation

It is the hyper-branching when proceeding from the centre of the dendrimer towards the periphery, which gives a homo-structural layers between the focal points or branching points. The number of focal points when going from the core to the dendrimer surface is the generation number. That is a dendrimer having five focal points when going from the centre or core to the periphery is denoted as the fifth generation dendrimer. Here, we abbreviate this
term to simply a G5-dendrimer, *e.g.* a fifth generation polypropylene imine is abbreviated to a “G5-PPI” dendrimer. The core part of the dendrimer is denoted generation “zero”, or presented “G0”. The core structure thus presents no focal points, as hydrogen substituents are not counted as focal points. Intermediates during the dendrimer synthesis are occasionally denoted half-generations, a well-renowned example is the carboxylic acid-terminated PAMAM dendrimers.

**Shell**
The shell of dendrimer is the homo-structural spatial segment between the focal points, the ‘generation space’. The ‘outer shell’ is the space between the last outermost branching point and the surface. The ‘inner shells’ are generally considered as the dendrimer interior.

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

**End-group**
It is also generally assigned to as the “terminal group” or the “surface group” of the dendrimer. Dendrimers having amine end-groups are called as “amino-terminated dendrimers”.

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**Synthesis of dendrimers**
Most synthesis of dendrimers involve the repetitive alternation of a growth reaction and an activation reaction. Often, these reactions have to be performed at many spots on the same molecule simultaneously. Clearly, the reactions must be high yielding and clean for the construction of large targets to be feasible. Many dendrimer synthesis rely upon conventional reactions, such as the Michael reaction, or the Williamson ether synthesis, whilst others involve the use of modern chemistry and techniques, such as solid phase synthesis, organotransition-metal chemistry, organo-phosphorous chemistry, organosilicon chemistry, or any current organic methodologies. The choice of the growth reaction shows the way in which branching is instilled into the dendrimer. Branching may either be present in the building blocks which is often the case or it can be introduced as a function of the growth reaction, as is the case with the PAMAMs and the polypropylene imine.[10-21]
Divergent' dendrimer growth
The synthetic procedure employed in the untimely dendrimer synthesis came to be called as the “divergent” approach. This name came from the way in which the dendrimer grows outer most from the core, diverging into space. A schematic representation of divergent growth is shown in figure:3. From the starting of a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers. The 2-steps can be repeated. The divergent approach is triumphant for the production of enormous quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is twice or doubled. Massive dendrimers have been prepared in this way, but halffly synthesized growth steps and side reactions lead to the characterisation and isolation of slightly faulty samples. Divergently grown dendrimers are practically impossible to isolate pure from their side products obtained. The synthetic chemist must rely on extremely efficient reactions in order to ensure low polydispersities.[22]

Convergent dendrimer growth
The 'convergent' approach emerged as a response to the weakness of divergent synthesis. A schematic representation of divergent growth is shown in figure:3. Convergent growth begins at a point what will end up being the surface of the dendrimer, and works inwards by constantly linking surface units together with additional monomers. When the growing blocks are big enough, several are attached to an appropriate core to give a entire dendrimer. Advantage of convergent growth over divergent growth evokes from the fact that only 2-simultaneous reactions are needed for any generation-adding step. Most importantly, this protocol makes the purification of ideal dendrimers easier. The growth reactions do not have to be so closely efficient, and it becomes possible to introduce subtle engineering into dendritic structure. The number of steps required to build up a large structure is not reduced as compared with the divergent approach, yet more starting material is required. The convergent methodology also bares low yields in the synthesis of larger structures. Dendritic blocks of higher generations encounter steric problems in reactions of their 'focal points'.

'Hypercores' and 'Branched' monomers[23]
Hypercores and branched monomers allow to devise synthetic strategies that are more convergent in the classical synthetic sense of the words. An interesting comparison of convergent, divergent, and hypercore synthesis of phenyl-acetylene dendrimers was done by Moore, but the solubility issues in the divergent steps made the convergent approach at favourable side.

Conventional approaches
Revised approaches

![Fig:4 Conventional and Revised Approaches](image)

Double exponential' and 'Mixed' growth [24]
The most recent fundamental revolutionary in the practice of dendrimer synthesis has come with the implications and concept of 'double exponential' growth. Double exponential growth, alike to that of rapid growth technique for linear polymers involves an AB2 monomer with orthogonal protecting groups for the A,B functionalities. This technique allows the preparation of monomers for both convergent and divergent growth from a sole starting material. These 2-products are reacted together to give an
orthogonally protected trimer, which may be used to recite the growth process again as shown in figure-4.

Types of dendrimers [25]

**Pamam dendrimer**

Polyamidoamine dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylene-di-amine initiator core reagents. Products upto generation 10(7)(molecular weight of over 9, 30,000 g/mol) have been attained. (in comparison, the molecular weight of human haemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, mostly as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-amino-ethylene-imine core. The name refers to the star like pattern observed when observed at the structure of the high-generation dendrimers of this type in two-dimensions.

**Pamamos dendrimer**

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

**PPI dendrimer**

PPI-dendrimers stands for “Poly (Propylene Imine)” describing the propylamine spacer moieties in the older known dendrimer type developed initially by Vögtle.(8) These dendrimers are generally poly-alkyl amines having 10-amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines. Polypropylene imine dendrimers are commercially available up to G5, and has found widespread applications in material science and also in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM denoted for Poly (Propylene Amine), which closely in resemblance with PPI. In addition, these dendrimers are also sometimes denoted “DAB-dendrimers” where DAB mentioned to the core structure, which is usually based on Diamino butane.

**Tecto dendrimer**

These consist of a core dendrimer, surrounded by dendrimers of several steps to perform a function for a smart therapeutic nano-device. Dissimilar compounds perform varied functions varying from, diagnosis of disease state drug delivery, diseased cell recognition, reporting location to reporting outcomes of therapy.

**Multilingual dendrimers**

The surface of these dendrimers contains various copies of a particular functionalities.

**Chiral dendrimers**

These are developed with two segregated areas of chain end, one of the half is electron donating and the remaining half is electron withdrawing.

**Micellar dendrimers**

These are uni-molecular micelles of water soluble hyper-branched poly-phenylenes.

**Multiple antigen peptide dendrimers**

It is a dendron like molecular synthesis based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a better monomer for the inoculation of numerous branching points.

**Fréchet-type dendrimers**

It is a more recent type of dendrimers discovered by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers mainly have carboxylic acid groups as surface groups, which serves as a good anchoring point for further surface fictionalization.

<table>
<thead>
<tr>
<th>Generation</th>
<th>Molecular weight (Daltons)</th>
<th>Diameter (A)</th>
<th>Surface groups (-NH2)</th>
<th>Radius of Gyration (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>517</td>
<td>15</td>
<td>4</td>
<td>4.93</td>
</tr>
<tr>
<td>G1</td>
<td>1430</td>
<td>22</td>
<td>8</td>
<td>7.46</td>
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<tr>
<td>G2</td>
<td>3256</td>
<td>29</td>
<td>16</td>
<td>9.17</td>
</tr>
<tr>
<td>G3</td>
<td>6909</td>
<td>36</td>
<td>32</td>
<td>11.2</td>
</tr>
<tr>
<td>G4</td>
<td>14215</td>
<td>45</td>
<td>64</td>
<td>14.5</td>
</tr>
<tr>
<td>G5</td>
<td>28826</td>
<td>54</td>
<td>128</td>
<td>18.3</td>
</tr>
<tr>
<td>G6</td>
<td>58048</td>
<td>67</td>
<td>256</td>
<td>22.4</td>
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<td>G7</td>
<td>116493</td>
<td>81</td>
<td>512</td>
<td>29.1</td>
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<td>G8</td>
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<tr>
<td>G11</td>
<td>1869780</td>
<td>167</td>
<td>8192</td>
<td>68.3</td>
</tr>
</tbody>
</table>

Table 1: Physiochemical Properties of PAMAM-NH2 Dendrimers (G0-G11)
and polar surface groups to enhance the solubility of this hydrophobic dendrimers type in polar solvents or aqueous media.

**Methods for characterization of dendritic polymer [26]**

The development of mass spectroscopic techniques such as MALDI and electrospray mass spectrometry has allowed the complete determination of dendrimer perfection. Mass spectrometric results on dendrimers, demonstrate the uniformity of the molecular mass and the extreme sensitivity of the technique. Scattering techniques is measure of an average of the spatial distribution of all of the units which is known as the radius of gyration (Rg) of dendrimers. Transmission electron microscopy (TEM) is usually used to image individual dendritic molecules, usually the larger generations. Recently, dendritic molecules are also imaged using atomic force microscopy (AFM).

Following methods can be used for characterization of dendritic polymers.

- **Spectrometry and Spectroscopy methods** like Infra-red (IR) and Raman, Ultra-violet-visible (UV-VIS), Chirality, Nuclear Magnetic Resonance (NMR), Circular dichroism (CD), Optical rotation, Fluorescence, Mass spectrometry and X-ray diffraction.
- **Scattering techniques** like, Small angle X-ray scattering (SAXS), Small angle neutron scattering (SANS) and Laser light scattering (LLS).
- **Electrical techniques** like Electrochemistry, Electron paramagnetic resonance (EPR) and Electrophoresis.
- **Size exclusion chromatography (SEC)**
- **Microscopy** like Transmission electron microscopy, Scanning electron microscopy and atomic force microscopy.
- **Rheology, physical properties** like intrinsic viscosity, Dielectric spectroscopy (DS) and Differential Scanning Calorimetry (DSC).
- **Miscellaneous** like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc.

**Applications**

**Dendrimers in Drug Delivery**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Routes of administration</th>
<th>Drug</th>
<th>Dendrimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IV</td>
<td>5-Fluorouracil phosphate</td>
<td>PEGylated PAMAM dendrimer Galactose-coated PPI dendrimer</td>
</tr>
<tr>
<td>2</td>
<td>IM</td>
<td>Doxorubicin</td>
<td>Polyester dendrimer</td>
</tr>
<tr>
<td>3</td>
<td>Transdermal</td>
<td>Artemether</td>
<td>PEGylated peptide dendrimer</td>
</tr>
<tr>
<td>4</td>
<td>Ophthalmic</td>
<td>Tamsulosin</td>
<td>PAMAM dendrimers</td>
</tr>
<tr>
<td>5</td>
<td>Oral</td>
<td>Indomethacin</td>
<td>PAMAM dendrimers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tropicamide</td>
<td>PAMAM dendrimers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5-Fluorouracil</td>
<td>PAMAM dendrimers</td>
</tr>
</tbody>
</table>

**Table 2: Dendrimers in drug delivery**

Polymer based drug delivery systems are designed to enhance the pharmacokinetics and bio-distribution of a drug and also provide controlled release kinetics to the proposed target. The ideal dendrimer carrier should exhibit drug loading capacity and high aqueous solubility, biodegradability, low toxicity, specificity, complimentary retention and biodistribution 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) using different dendrimers and routes of administration.[27]

**Dendrimers as Ophthalmic Vehicles**

Some current research efforts in dendrimers for ocular drug delivery involve PAMAM dendrimers that were studied by Vandamme and Brobeck for controlled delivery of pilocarpine and tropicamide to the eye as ophthalmic vehicles.[30] 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.[30] In another study, dendrimer end groups were conjugated with aminosaccharides and sulphated aminosaccharides to acquire anionic dendrimers with distinctive biological properties.[28]

**Dendrimers in pulmonary drug delivery**

Dendrimers have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation are positively charged PAMAM dendrimers improved the relative bioavailability of Enoxaparin by 40%. [29]

**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 Pgp efflux transporter does not affect dendrimers, therefore drug dendrimer complexes are capable to bypass the efflux transporter. PAMAM dendrimers conjugated with the fluorescein isothiocyanate and folic acid for targeting the tumor cells and imaging it respectively.
assembled dendrimer conjugates may permit the combination of different drugs with different targeting and imaging agents so combinatorial therapeutics is easy to develop.[30]

**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). 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 design 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.[31]

**Topical and Transdermal Delivery:**[32-33]

![Fig 5: Transdermal drug delivery](image)

Dendrimers have established recent applications in novel topical and transdermal delivery systems, providing benefits such as drug-polymer conjugates (pro-drugs), improved drug solubilisation and also controlled release. For ease of handling, 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), anticancer, antimicrobial, antiviral, or antihypertensive drugs. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAIDs are ketoprofen and diflunisal. Also transport of indomethacin through intact skin was enhanced *in vitro* and *in vivo* has been studied earlier. 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 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.

**DENDRIMERS IN THERAPEUTICS:**

**Dendrimers in Gene Therapy**[34-35]

![Fig6: Gene delivery by Dendrimers](image)
Gene delivery of effective non-viral vectors 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. By scanning force microscopy data it is observed that DNA wraps around the dendronized polymers. In recent reports, electroporation and addition of β-cyclodextrin were combined with DNA–dendrimer systems. Electroporation caused significant enhanced in gene expression and addition of β-cyclodextrin caused development of smaller and more monodisperse particles. 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. Poly(ethylene glycol) functionalization of G(5)-PAMAM dendrimers formed a 20-fold increase in transfection efficiency using plasmid DNA coding for reporter protein β-galactosidase relative to partially degraded PAMAM dendrimers. Some of the polycation–DNA complexes are 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.

**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 encloure 10-hydroxycamptothecin (10-HCPT) for delivery to cancer cells. 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. The anticancer drugs doxorubicin and etoposide were encapsulated dendrimer systems. 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 needed for encapsulation and solubilisation of hydrophobic drugs. Paclitaxel solubilities ranged from 80–128 μg/mL with gradual increasing generations from G3–G5 of poly (glycerol), or three orders of magnitude higher than free paclitaxel. Melamine-based dendrimers were used to solubilize the anticancer drugs 6-mercaptopurine and methotrexate, as well as to reduce drug toxicity. Therapeutic agents are internalized by micellar formation of the dendrimers or within the interior core space. A major drawback to these delivery systems is deficiency 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.[36]

**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 and every dendrimer molecule and the release of these therapeutic molecules is partially controlled by nature of the linkages. The Kanann group reported, the synthesis of PAMAM-methotrexate conjugates obtained from the carboxylic acid or amine group...
in order to check the activity of methotrexte in human acute lymphoblastoid leukemia and Chinese hamster ovary cell line indicates the potential of dendrimer drug conjugates for the treatment of cancer cells. Paclitaxel was conjugated to G4-PAMAM or PEG to estimate the anti-cancer activity of the drug delivered by a linear or dendritic carrier. Doxorubicin-G4-PAMAM complexes have been encapsulated into liposomal formulations for potential local delivery to sites such as skin metastasis from breast cancer. It is clear that dendrimer-drug conjugates are highly capable of delivering a payload with required bioavailability to achieve a therapeutic goal. The release of covalently linked drug depends on the chemical linkage binding the agent to the carrier. Novel structures of dendrimer are synthesized to furthermore explore finer control of release kinetics.

**Dendrimer in HIV and HSV Infection [39]**

Dendrimer are useful to inhibiting the entry of HIV and herpes simplex virus (HSV) types 1 and 2. Dendrimer compound VivageTM, inhibit the replication of HIV-1 (Strain IIIB) in a range of cells types with an EC50 of <1μg/mL. The compounds were not toxic to the cells upto the elevated concentration. Dendrimers are also effective in protecting primary foreskin fibroblast cells in-vitro from the cyto-pathic reactions 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 representative dendrimer– SPL2999 Dendrimer SPL7013 which possessed both a high level and wide range of activity against HSV and HIV.

**Diagnostic application of Dendrimer[36-42]**

**Dendrimers as molecular probes**

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

**Dendrimers as X-ray contrast agents**

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

**Dendrimers as MRI contrast agents**

Various 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. To enhance 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 folic acid folate conjugated Gd(III)-DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells which expresses the high affinity folate receptor. Recently, the mix use of paramagnetic chelates and fluorescent groups attached to the surface of the PAMAM dendrimers have enabled dual-mode imaging of lymph nodes by both MR imaging and fluorescence microscopy.

**Detection of Molecules with Biological Importance:**
Modified surfaces with nanostructured composition of Prussian Blue (PB) and dendrimers represent some of the most promising approaches for the development of effective and recent materials for advanced electrochemical applications. As the Prussian Blue interacts in supra-molecular process with PAMAM dendrimers in aqueous medium, across the hydrophobic zone of dendrimers, they form composites stable in solution with different generations of PAMAM. Dendrimers make the function of endoreceptors of PB forming composition 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 electrostatically modified electrodes. A simple DNA biosensor according to the application of dendrimer is developed. This work shows that the dendrimer-DNA compatibility, exploited in the field of gene delivery.

**Dendrimer as solubility enhancer**
Uni-molecular micellar nature of dendrimers is due the hydrophilic interiors and hydrophobic exteriors. They form covalent plus non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour. ChengYiyun et al worked on solubilization of NSAID drugs in the presence of polyamidoamine dendrimers and results unveiled that the solubility of NSAIDs in the PAMAM dendrimer solutions was nearly proportional to dendrimer concentration.

**Dendrimer in market**
In July 2003 the FDA allowed the first clinical trials of a dendrimer based pharmaceutical: vivagelTM which is vaginal gel to prevent HIV. Nowadays so many products like StratusTMCS used as cardiac marker prepared by Dade Behring, SuperfectTM used for gene transfection made by Qiagen and Alert TicketTM prepared by US Army Research Laboratory used for anthrax detection based on dendrimer accessible in market. 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. The Swedish company perstorp sells dendrimerlike 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 AvidimersTM (Avidimer Therapeutics, Ann Arbor, MI) for cancer prevention and treatment and gadolinium-based MRI contrast agent.[30]Starpharma, in collaboration with its US-based wholly owned company Dendritic Nanotechnologies (Mount Pleasant, MI) recently announced the commercial launch of its PriostarTM dendrimer-based technology research product called the Nanofluorescence Transfection Kit in addition to the Starburst and Priostar-based dendrimer family.[30]Because of the presence of large numbers of functional groups, these highly branched dendrimers have capacity to bind with DNA. They will be useful for transfection of DNA into the variety of difficult-to-transfect cells.

**References**


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