DENDRIMERS: SYNTHESIS, ITS DOSAGE FORMS AND ADVANTAGE OVER LINEAR POLYMERS

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ABSTRACT

Objective: The main objective of this study is to improve existing therapies and find new drugs based on dendrimers. Nanoparticle drug-delivery systems are able to increase the selectivity and stability of therapeutic agents. However reticuloendothelial system (RES) uptake, drug leakage, immunogenicity, hemolytic toxicity, cytotoxicity, hydrophobicity restrict the use of these nanostructures. These shortcomings are overcome by surface engineering by the dendrimer such as Polyester dendrimer, Citric acid dendrimer, Arginine dendrimer, Glycodendrimers, PEGylated dendrimers, etc.

Conclusion: From this present review study, we concluded that 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.

Keywords: Dendrimers, Synthesis, Dosage Forms, Characterization, Functions & its importance.

INTRODUCTION

A dendrimer is generally described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers have often been referred to as the “Polymers of the 21st century”. The word “dendrimer” originated from two words, the Greek word Dendron, meaning tree, and meros, meaning part. 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 term cascade molecule is also used, but ‘dendrimer’ is the best established one. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy. Dendrimers are branching molecules with the branching beginning at the core. [1] Depending on the core, the dendrimer can start with 3 to 8 (or more) branches, with 3 and 4 being the most common number. Starting from the core, the dendrimer consists of long chains of atoms with a branch point about every half dozen atoms. At each branch point, the current chain of atoms becomes two chains of atoms. The molecular structure has the form of a tree with a great number of branches.

Fig.1: Dendrimers: A novel drug delivery system

STRUCTURE

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator. Dendrimers possess three distinguished architectural components, namely

(i) An initiator core.

(ii)Interior layers composed of repeating units, radically attached to the interior core.

(iii) Exterior (terminal functionality) attached to the outermost interior generations.

Fig.2: The Dendritic Structure [2]

TYPES OF DENDRIMERS [3]

PAMAM Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core.

PAMAMOS Dendrimers

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

PPI Dendrimer

PPI-dendrimers stand for “Poly (Propylene Imine)” PPI dendrimers are commercially available up to G5, and has found widespread
applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine).

**Tecto Dendrimers**
These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice.

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

**Chiral Dendrimers**
The chirality in these dendrimers are based upon the construction of a constitutionally different but chemically similar branches to chiral core.

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

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

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

**SYNTHESIS**
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. Three types of dendrimers are formed [4].

**‘Divergent’ Dendrimer Growth**
This name comes from the way in which the dendrimer grows outwards from the core, diverging into space. Divergently grown dendrimers are virtually impossible to isolate pure from their side products. The first synthesized dendrimers were polyamidoamines (PAMAMs).

**‘Convergent’ Dendrimer Growth**
The ‘convergent’ approach was developed as a response to the weaknesses of divergent syntheses. Convergent growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step.

a. Relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised.

b. Possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecules.

c. Approach does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.

**‘Double Exponential’ And ‘Mixed’ Growth**
The most recent fundamental breakthrough in the practice of dendrimers synthesis has come with the concept and implications of ‘double exponential’ growth. A schematic representation of double exponential and mixed growth. 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 trimer, which may be used to repeat the growth process again.

**Fig. 3: synthesis process of dendrimers [5]**

**Fig 4: double exponential synthesis method of dendrimers [6]**
Properties of dendrimers over linear polymers

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Property</th>
<th>Dendrimers</th>
<th>Linear Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Structure</td>
<td>Compact, Globular</td>
<td>Not compact</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis</td>
<td>Careful &amp; stepwise growth</td>
<td>Single step polycondensation</td>
</tr>
<tr>
<td>3</td>
<td>Structural control</td>
<td>Very high</td>
<td>Low</td>
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<td>4</td>
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<td>Random coil</td>
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<td>Crystallinity</td>
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<td>Semi crystalline/crystalline materials</td>
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<td>-lower glass temperatures</td>
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<td>Nonpolar solubility</td>
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<td>Viscosity</td>
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<td>Linear relation with molecular weight</td>
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<td>Reactivity</td>
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<td>12</td>
<td>Polydispersity</td>
<td>Monodisperse</td>
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Method of Characterization for Dendrimers

- Spectroscopy and spectrometry methods like Nuclear Magnetic Resonance (NMR), Infrared (IR) and Raman, Ultra-violet-visible (UV-VIS), Fluorescence, Chirality, Optical rotation, Circular dichroism (CD), X-ray diffraction, and Mass spectrometry
- Scattering techniques like Small angle X-ray scattering (SAXS), Small angle neutron scattering (SANS), and Laser light scattering (LLS)
- Electrical techniques like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis
- Size exclusion chromatography (SEC)
- Microscopy like Transmission electron microscopy, Scanning electron microscopy and atomic force microscopy
- Miscellaneous like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimentry etc.[8,9,10]

Dosage Forms of Dendrimers

Cosmetics and personal care applications

Because of their excellent carrier properties, dendrimers have utility in cosmetics and personal care products such as hair-styling gels, shampoos, sunscreens, and anti-acne products. Cosmetic compositions comprising hydroxyl-functionalized dendritic macromolecules are described in a patent filed by Unilever's Home & Personal Care division. Another patent filed by L'Oreal described terminal hydroxyl functional group polyester dendritic macromolecules in combination with film-forming polymers for use in cosmetic and dermatological products intended for application to the skin, keratinous fibers, nails, or mucous membranes.[11] Such a combination of a film-forming polymer with a dendritic polymer allowed the inventors to develop a low-viscosity product that was easily applied to the intended topical skin site and that formed a dry film capable of being peeled-off after the application period.[8,9,10]

Dendrimers as ophthalmic vehicles

The majority of topically applied ocular drug-delivery systems are formulated either as solutions, ointments, or suspensions and suffer from various disadvantages such as quick elimination from the precorneal region, poor bioavailability, or failure to deliver the drug in a sustained fashion.[12,13] Several research advances have been made in ocular drug delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome some of these disadvantages. Some recent 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.

FUNCTION OF DENDRIMERS

In August 2000, we began tests in vivo. The in vivo tests are to confirm that the nano-devices will work as therapeutic agents.[15, 16]

- Diseased cell recognition
- Diagnosis of disease state
- Drug delivery
- Reporting location

Advantages of Dendrimers over Other Novel Drugs

- Biocompatibility.
- Non-toxicity.
- Non-irritability.
- Thermodynamically stable in the body.
- Ability to reach places in the body inaccessible to more massive red blood cells.
- High solubility in water.
- High oxygen solubility.
- Efficient rate of oxygen transfer into an aqueous phase.

The greatest advantage of dendrimers technology is possibly the potential for very cost-effective manufacturing. Because dendrimers are not derived from human or animal sources and manufacturing techniques are relatively simple and thoroughly established, if a dendrimer was identified that was an effective hemoglobin substitute the cost of manufacturing would be dramatically less than that of current HBOCs and even transfused blood.[17, 18, 19]
APPLICATIONS

Pharmaceutical Application

Dendrimers Drug Delivery: Targeted And Controlled Release Drug Delivery

Dendrimers have attracted attention as possible drug carriers because of their unique properties namely their well defined three-dimensional structure, the availability of many functional surface groups, their low polydispersity and their ability to mimic. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug) [20].

Noncovalent Encapsulation of Drugs / Host –Guest Relation

Encapsulation of drugs use the satric bulk of the exterior of the dendrimer or interactions between the dendrimer and drug to trap the drug inside the dendrimer. Maciejewski introduced the concept of encapsulating guest molecules into special, egg-shell-like structures. Such a system can be used to encapsulate drugs and provide controlled delivery. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications [21].

Covalent Dendrimer–Drug Conjugates

An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for the covalent attachment of drug molecules to the dendrimers periphery. In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids. Conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with non-specific toxicity and poor water solubility [22, 23].The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors.

Dendrimer as Solubility Enhancers

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers having a hydrophobic core and a hydrophilic surface layer, have been termed unimolecular micelles. A hydrophilic–hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-fluorouracil, a water-soluble anti-tumor drug [24].

Cellular Delivery Using Dendrimer Carriers

Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexed drug inside cells [25]. PAMAM dendrimers were surface-engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

Dendrimers As Nano-Drugs

Poly(lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs). Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications [26, 27].

Dendrimers In Photodynamic Therapy

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes .Photos entisive dyes have been incorporated into dendrimers and utilized in PDT devices[28]. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

Dendrimers In Gene Transfection

Dendrimers can act as vectors, in gene therapy, PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus [29, 30]. A transfection reagent called SuperFectTM consisting of activated dendrimers is commercially available.

Non-Pharmaceutical Application

Diagnostics

Paramagnetic metal chelates such as Gd(III)-N,N’N”N”-tetracarboxymethyl-1,4,7,10-tetraazaacyl-clocodocadene (Gd(III)-DOTA), Gd(III)-diethylene tri-amine pentaacetic acid (Gd(III)-DTPA), and their derivatives used as contrast agents for magnetic resonance imaging(MRI). DNA-dendrimers, which are constructed for routine, use in high-throughput functional genomics analysis, and as biosensors for the rapid diagnosis have genetic, and pathogenesis diseases [31].

Dendritic Catalysis / Enzymes

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture [32, 33, 34, 35].

- Metalloendritic catalysts.
- Catalysis with phosphine-based dendrimers.
- Catalysis with (metallo) dendrimers containing chiral ligands.
- Non-metal containing dendrimers.

Industrial Processes

Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior [36, 37]. Cooper and co-workers synthesized fluorinated dendrimers, which are soluble in supercritical CO₂ and can be used to extract strongly hydrophilic compounds from water into liquid CO₂.

Sensors

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using poly (propyleneimine), cadmium - sulfide /polypropyleneimine tetradezamaine dendrimers composites to detect fluorescence signal quenching [38, 39, 40].

CONCLUSION

The dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight, thereby offering new scaffolds for drug delivery. An increasingly large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimers based drug delivery systems.

REFERENCES


