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DENDRIMER: A SMART POLYMER

ABSTRACT

Dendrimers are macromolecules having highly branched, 3D structure, nanoscale architecture with monodispersity and high functionality. These features make it attractive candidates as drug carriers for controlled release or targeted delivery. Encapsulation offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability. Dendrimer is a smart polymer having various applicability in pharmaceutics, industry and diagnosis. This review covers the points of synthesis, types, properties, encapsulation, applications, characterisation etc.

Key words: Dendrimer, biocompatible, encapsulation, polydispersity

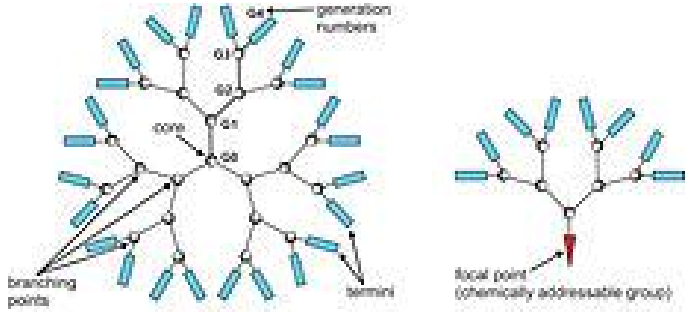
DEFINITION

Dendrimers are synthetic macromolecules having highly branched, three dimensional, nanoscale structure with very low polydispersity and high functionality

INTRODUCTION

The word "dendrimer" originated from two words, the Greek word dendron, meaning tree, and meros, meaning part (11). Dendrimers are characterized by its highly branched 3D structure (5) It is mono-dispersed polymer having 5-10 nanometers in diameter (1) dendrimers have a high degree of molecular uniformity, narrow molecular weight distribution, specific size and shape characteristics, and a highly- functionalized terminal surface. (2) It is mainly act as carrier in solubilization applications, delivery of DNA and oligonucletide, targeting drug at specific receptor site. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular [3]. Dendritic architecture accommodates chemically diverse types of core and subunit compositions, allowing the control of surface chemistry/composition, and giving further control of particle size, topography and shape.(4)

An increasingly large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability, biocompatibility and toxicity dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs with reduced cost of its production .(5)



DENDRIMER DENDRON

Dendritic molecules are characterized by structural perfection. Dendrimers and dendrons are monodisperse and usually highly symmetric, spherical compounds. The field of dendritic molecules can be roughly divided into low-molecular weight and high-molecular weight species. The first category

includes dendrimers and dendrons, and the latter includes dendronized polymers, hyperbranched polymers, and the polymer brush. The properties of dendrimers are dominated by the functional groups on the molecular surface, however, there are examples of dendrimers with internal functionality (6, 7, 8). Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials.

PROPERTIES

(1) Dendritic polymers that can be constructed with a well-defined molecular structure, i.e. being mono-disperse, unlike to linear polymers.
(2) Nanoscale sizes that have similar dimensions to important bio-building blocks, e.g., proteins, DNA.
(3) When dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) show non or low-immunogenicity.
(4) Ability to arrange excretion mode from body, as a function of nanoscale diameter.
(5) An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties, reduces the drug toxicity and facilitates controlled release.
(6) Numbers of terminal surface groups suitable for bioconjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.
(7) Surfaces that may be designed with functional groups to resist trans-cellular, epithelial or vascular bio permeability.
(8) Dendrimers are monodisperse macromolecules. Size and molecular mass of dendrimers can be specifically controlled during classical polymerization process.
(9) When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a
maximum at the fourth generation and then begins to decline.
(10) The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity.
(11) Dendrimer solubility is strongly influenced by the nature of surface groups.
(12) The dendrimer should be: nontoxic, on-immunogenic, able to cross bio barriers (biopermeable), able to stay in circulation for the time needed to have a clinical effect and able to target to specific structures. (9, 10)

STRUCTURE OF DENDRIMER

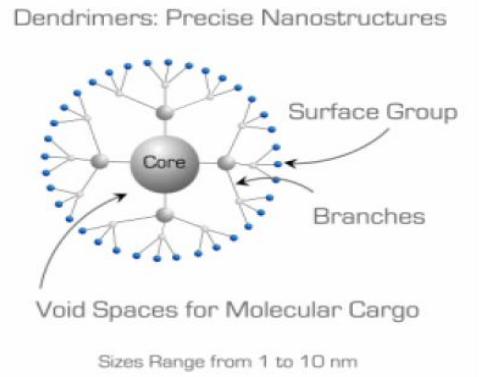


Figure. Schematic representation if a generation 2 dendrimer

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 produces 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.

Dendrimer mainly having following parts:

1. A central core, which is either a single atom or an atomic group.
2. Branches emanating from the core composed of repeating units called generation, which is radially in position.
3. Many terminal functional group generally located in the exterior of the macromolecule

(12, 13)

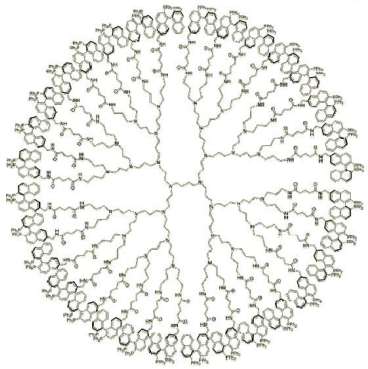


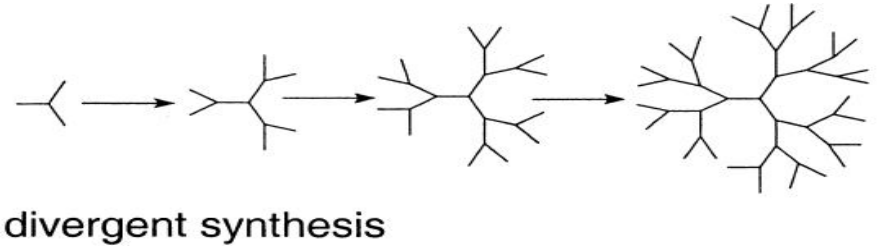
Figure. Highly branched three dimensional structures

As the chains growing from the core molecule become longer, more branched, and higher dendrimers adopt a globular structure. 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. (14)

SYNTHESIS OF DENDRIMER

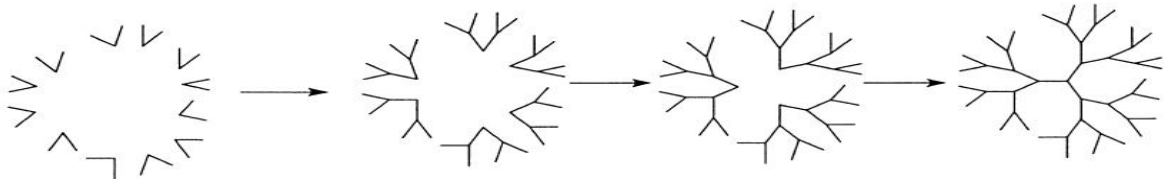
1) **Divergent growth method:**

The core molecule first interacts with a monomer molecule containing one reactive and two non-reactive groups, which allows additional monomers to attach [15]. This process is repeated a number of times until a 'starburst' formation has occurred with a multitude of
branches to create a dendrimer. Divergently grown dendrimers are virtually impossible to isolate pure from their side products (5)



2) Convergent growth method:

In the convergent preparation, the dendrimer is constructed piece by piece, starting from the outside sections and working inwards. Polymeric branches are grown originally independent of the core centre until they are large enough to be attached to the multifunctional core molecule(16) The convergent methodology also suffers from low yields in the synthesis of large structures



convergent synthesis

(3) Double Exponential and Mixed Growth:

In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps (16, 17)

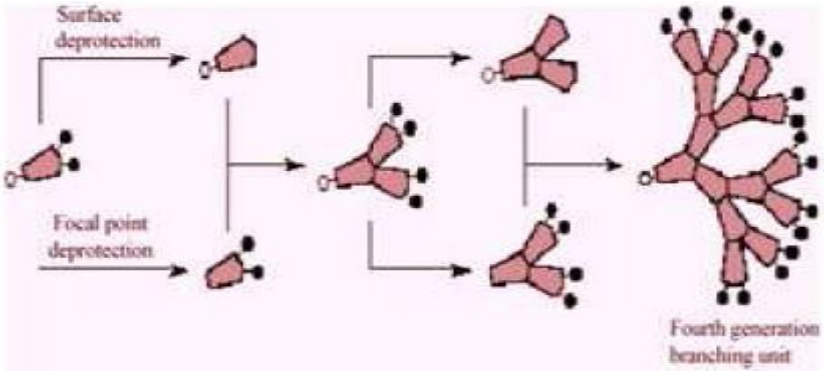


Fig.Double exponential growth

(4) Hypercores and Branched Monomers growth:

This method involved the pre-assembly of oligomeric species which can be linked organic methodologies

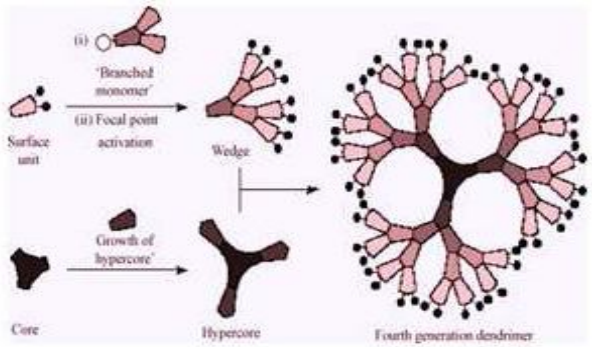


Fig. Hypercores and branched monomers growth

Types of dendrimer:

1) Chiral dendrimer:

Preparation of optically active dendrimers stemmed from their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis (18)

(2) Poly (amidoamine) dendrimers (PAMAM):

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. They are commercially available as methanol solutions and ingeneration G 0-10 with 5 different core type and 10 functional surface groups. (19, 20)

(3) Liquid crystalline dendrimers:

A highly branched olegomers 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.

(4) 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.

(5) Hybrid dendrimers:

Hybrid dendrimers are hybrids 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.

(6) Multilingual Dendrimers:

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

(7) Micellar Dendrimers:

Micellar dendrimers are unimolecular water-soluble hyper branched polyphenylenes micelles.

(8) Poly (Propylene Imine) dendrimers (PPI)

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

Encapsulation of drugs within dendrimer:

Encapsulation offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability and controlling its release. The nature of drug encapsulation within a dendrimer may be simple physical entrapment, or can involve non-bonding interactions with specific structures within the Dendrimer (21, 22)

(1) Unimolecular micelles:

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. lipophilic probes were located within the lipophilic infrastructure of the dendritic

structures and it was concluded that the polymers exist as single molecules capable of molecular inclusion and therefore act as unimolecular micelles (25-26)

(2) PEGylated dendrimers:

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer to provide a hydrophilic shell around a hydrophobic dendritic core to form a unimolecular micelle. Because of its high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications. (27, 28)

(3) Dendritic box:

During the synthetic process, guest molecules could be entrapped within the cavities of the

dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication and yield a dense and rigid chiral shell with solid-phase properties and a flexible core capable of entrapping molecules.

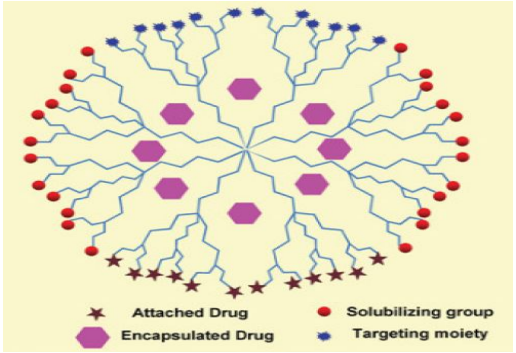


Figure 3. Dendritic box encapsulating guest molecules

(4) Cored dendrimers:

The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups. (29, 30)

Surface interactions between drug and dendrimer:

The external surfaces of dendrimers have been investigated as potential sites of interaction with drugs.

(1) Electrostatic interaction between drug and Dendrimer:

The presence of large numbers of ionisable groups on the surface of dendrimers provides an interesting opportunity for electrostatic attachment of numerous ionisable drugs, providing the resultant complex retain sufficient water solubility. Electrostatic interaction can occur between the carboxyl groups of this weakly acidic drug and the amine groups of the dendrimers. (31)

(2) Conjugation of drug to dendrimer:

The covalent attachment of drugs to the surface groups of dendrimers through hydrolysable or biodegradable linkages offers the opportunity for a greater control over drug release. (32, 33)

Characterizations of dendrimer:

1) Spectroscopy techniques:

a) NMR:

It is mainly used for analysis of Size, Morphology and Dynamics of Dendrimers for organic dendrimers such ad PPI, polyphenylester.

b) **UV-Vis method:**

Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units.

c) **Infra red spectroscopy:**

For routine analysis of the chemical transformations occurring at the surface of dendrimers.

d) **Fluorescence:**

The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers.

e) **Mass spectroscopy:**

Electrospray ionization can be used for dendrimers able to form stable multicharged species.

f) **X-ray diffraction:**

This technique should allow precise determination of the chemical composition, structure, size and shape of dendrimers

2) Microscopy:

Transmission microscopy and Scanning microscopy are mainly used for dendrimer analysis.

3) **Chromatography:**

Size exclusive or gel permeation chromatography allows the separation of molecules according to size.

4) **Electrical techniques**

Electron paramagnetic resonance, electrochemistry, electrophoresis are used.

5) **Rheology, Physical properties:**

Used to detect the glass transition temperature, which depends on thy molecular weight, entangment and chain composition of polymers. (41)

APPLICATIONS OF DENDRIMER

1) Dendrimer in ocular drug delivery:

Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability. (31, 32)

2) Dendrimers in pulmonary drug delivery-

G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40 %. (33)

3) Dendrimer in transdermal drug delivery:

Dendrimers designed to be highly water soluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently.

4) 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, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. (39)

5) Dendrimers in targeted drug delivery:

One of the most effective cell specific targeting agents delivered by dendrimers is folic acid and methotrexate. DNA assembled dendrimer conjugates may allow the combination of

different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics (40)

6) Dendrimers for controlled release drug delivery:

PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5-fluorouracil.

Encapsulation of 5-fluorouracil into G=four increase in the cytotoxicity and permeation of dendrimers.

7) Dendrimer in tumor drug devery:

Dendrimers, which are capable of interacting specifically with cancerous tumor tissue, are an excellent option as a drug transporter within the body. Dendrimers also have an exceptionally high drug loading capacity, which provides a greater accumulation of drug at the tumor site.

8) Dendrimers in gene delivery:

Dendrimer-based transfection agents have become routine tools for many molecular and cell biologist's dendrimers are extensively used as non-viral vector for gene delivery .(41)

9) Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular Micellar nature. They form covalent as well as noncovalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour.

10) 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. This cancer treatment involves the

Administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

11) Dendrimers as X-ray contrast agents:

Number of potential dendritic X-ray contrast agents using various organometallic complexes such as bismuth and tin. (43, 44)

12) Dendrimers as MRI contrast agents:

To improve the pharmacokinetic properties of dendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast agents have been considered. (11)

13) Dendrimers in Nanobiological devices

Dendrimers are well suited for use in many nanobiological devices. They are highly monodisperse, and while expensive on a per gram basis compared to other synthetic macromolecules, are less expensive per unit mass than commercially produced proteins.

1) 14) Blood substitution:

Dendrimers are also being investigated for use as blood substitutes. . Their steric bulk surrounding a heme-mimetic centre significantly slows degradation compared to free heme and prevents the cytotoxicity exhibited by free heme. (44, 45)

MARKETED AVAILABLE DENDRIMERIC PRODUCTS

PRODUCT	APPLCATION	COMPANY
Vivagel	Vaginal Gel for preventing HIV	Starpharma
Stratus CS	Cardiac Marker	Dade Behring
SuperFect	Gene Transfection	Qiagen
Alert ticket	Anthrax Detection	US Army Research Laboratory

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