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Review Article

DESIGN, DEVELOPMENT, CHARACTERIZATION AND APPLICATIONS OF DENDRIMERS AS TARGETED DRUG DELIVERY SYSTEMS – REVIEW

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ABSTRACT

Dendrimers are high degree of branching, multivalency, globular architecture and well-defined molecular weight; make them promising new scaffolds for drug delivery. In the past decade, research has increased on the design and synthesis of biocompatible dendrimers and their application into many areas of bioscience including immunology and the development of vaccines and drug delivery like antimicrobials and antiviral and anticancer bio active agents. Dendrimers contain a very large number of reactive terminal functional groups that have been utilized to covalently couple a large variety of molecules, including proteins, specific disease cell receptors. Dendrimers may be engineered to meet the specific needs of biologically active agents, which can either be encapsulated within dendrimers or chemically attached to these units. Unique properties of uniform size, water solubility, modifiable surface functionality and availability of internal cavities makes them intriguing carrier for biological and drug delivery system. In the present review, we focused on the bioactive agents that can be easily encapsulated into the interior cavity (or) chemical attachment, conjugation (or) physically adsorbed on to the dendrimer surface to serve the desired properties of the carrier to cater specific needs of the active components, its characterization and application

INTRODUCTION:

Drug delivery is an important aspect of formulation as it is a proper choice that enhances the bioavailability, enhances the solubility, targets the action and reduces the toxicity.One of the main approach, which focuses on the above criteria, is Dendrimers[1].

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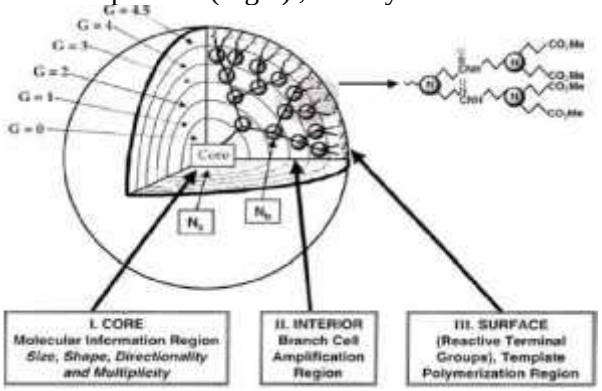
The word “dendrimer” originated from two words, the Greek word “dendron”, meaning tree, and “meros”, meaning part. Dendrimers are different from traditional polymers in that they have a multi-branched, threedimensional architecture with very low polydispersity and high functionality**.** Dendrimer is a nanoparticle based drug delivery system, which are macromolecules of highly symmetrical, hyper-branched, globular structure and monodisperse structure consisting of tree-like arms or branches[1,2]**.** They have architecture of

- Core-determines the size and shape of the dendrimer
- An interior of shells-determines the amount of the void space that can be enclosed by the dendrimer

- An exterior layer-allows growth of the dendrimer (or) other chemical modification.

Structure of A 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 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[3]. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex[4]. Dendrimers possess three distinguished architectural components (Fig:2) , namely:



Three Dimensional Projection Of Dendrimer Core-Shell Architecture For G=4.5 Pamam Dendrimer With Principal Architectural Components (I) Core, (Ii) Interior & (Iii) Surface

Components of a Dendrimer Structure:

Generation:

It is the hyper branching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points). The number of focal points when going from the core towards the dendrimer surface is the generation number. That is a dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer. Here, we abbreviate this term to simply a G5-dendrimer, *e.g*. a 5th generation polypropylene imine is abbreviated to a "G5-PPI-" dendrimer, The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented here "G0". The core structure thus presents no focal points, as hydrogen substituents are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted half-generations[5-8]

Shell : The dendrimer shell is the homo-structural spatial segment between the focal points, the "generation space". The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred to as the dendrimer interior.

Pincer: In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface.

End-group: It is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "amino-terminated dendrimers".

TYPES OF DENDRIMER[9-14]

(1)Radially layered poly (amidoamineorganosilicon) Dendrimers(PAMAMOS): In 1990, Dr.PetarDvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilicpolyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent itsnetworks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, electronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honeycomblike networks with nanoscopic PAMAM and OS domains.

(2) Poly (amidoamine) dendrimers(PAMAM)

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

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

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

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

(6) Tectodendrimer: TectoDendrimer are composed of a core dendrimer, perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

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

(8) Multilingual Dendrimers: Multilingual Dendrimers contains multiple copies of a particular functional group on the surface.

(9) Micellar Dendrimers: Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

SYNTHESIS OF DENDRIMER[15-25]

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 . 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

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

(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

(4) Hypercores and Branched Monomers growth:

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

Characterizations of dendrimer[23-33]: 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.

APPLICATIONS[34-44]

Ocular drug delivery

Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability.

Pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery of enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of enoxaparin by 40%.

Transdermal drug delivery

Dendrimers designed to be highly water soluble and biocompatible materials that have been shown to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen and Diflunisal) improved drug permeation through the skin.

Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. PAMAM dendrimers enhanced bioavailability of indomethacin through transdermal drug delivery.

Oral drug delivery

Oral drug delivery studies using the human colon adenocarcinoma cell line have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, PGP efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter. As increase in the concentration and generation, there was and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. 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.

As a controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G3 and G4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construction involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5-fluorouracil. Encapsulation of 5-fluorouracil into G4 increases in the cytotoxicity and permeation of dendrimers.

Targeted drug delivery

Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid PAMAM dendrimers modified with carboxy methyl PEG-5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. A third-generation dendritic unimolecular micelle with indomethacin showed a sustained *in vitro* release, as compared to cellulose membrane control. Controlled release of the flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM dendrimers. The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to un-encapsulated drug.

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. The use of dendrimers as gene transfection agents and drug-delivery devices has been extensively reviewed. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

As a solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behavior.

Cellular delivery

Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug, revealing that dendrimers can efficiently carry the complexes drug inside cells. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

Therapeutic application of dendrimers

Dendrimers in photodynamic therapy

The photosensitizer 5-amino levulinic 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.

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 10B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. 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.

Diagnostic applications

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.

Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools in medicine, and is applicable to numerous diseases. 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. 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.

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 coworkers developed a series of Gd(III)–DTPA-based PAMAM dendrimers. To improve the pharmacokinetic properties ofdendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast agents have been considered. Synthesized a folate conjugated Gd(III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

Cosmetic applications of dendrimers

Dendrimers owing to their highly branched nature have been widely used in the cosmetic industry. As they possess large number of external groups, which serves as a multifunctional properties as cosmetic agent carrier. Due to their hyperbranched nature they form a film upon deposition on a substrate and widely useful for variety of cosmetics eg. mascura and nail-polish. Hydroxyl functionalized dendrimers obtained from polyester units are capable for formulating sprays, gels or lotions. Several patients have been filed for dendrimers for artificial skin tanning, hair care, skin care and nail care products. The dendrimers possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight makes dendrimer ideal carriers for the various applications like drug delivery, therapeutic and diagnostic agent. A large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers is one of the drug delivery to overcome problems associated with drugs. Besides these problems they also help to overcome the problem of biocompatibility and toxicity. This review clearly illustrates the various aspects of dendrimer as a novel technique for drug delivery system. A large number of drugs being developed today are 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 overcome by careful surface engineering. Dendrimers due to its superior architecture; high level of branching, multivalency, globular architecture and molecular weight, prove to be a novel and reliable method of drug delivery. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production.

CONCLUSION

Dendrimer drug delivery systems are getting huge interest as an advantageous solution for delivering bioactive like drugs and gene. They provide a platform for the attachment of drugs or genes and their release through several mechanisms. Various applications of dendrimers have been explored during last three decades. Development in controlled polymerization and synthesis techniques have led to the emergence of well-controlled dendrimers structures with a large number of surface groups that can be utilized to display a range of biological molecules including peptides, proteins, sugars and targeting agents. The high loading capacity of dendrimers renders them highly attractive as carriers for delivery of chemotherapeutic agents. PEGylated and non-PEGylated dendrimers proved to encapsulate hydrophobic drug molecules into the hollow voids of their branching architecture, which enhance the aqueous solubility and stability of the encapsulated drug molecules. Both targeted and nontargeted dendrimer-drug complexes successfully penetrate across tumor's leaky vasculature and accumulate in the cancer tissue. However, targeted dendrimer-drug complexes have the added advantage of selectively binding to the receptors displayed on the surface of cancer cells, which increases their residence time on the cell surface and enhances their internalization kinetics into the cell.

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