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Dendrimers: Is An Novel Drug Delivery System:A Review

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ABSTRACT

Dendrimers are a new class of polymeric materials. A dendrimer described as a macromolecule characterized by its highly branched 3D structure which provides a high degree of surface functionality and versatility. Drugs are delivered through nanotubes in therapy, and specifically in the treatment of cancerous tumors. Dendrimers' unique characteristics such as hyper branching, well-defined spherical structure, and high compatibility with the biological systems are responsible for their wide range of applications including medical and biomedical areas. This review briefly discusses the various aspects of dendrimers including introduction, needs of dendrimer, advantages, disadvantages, properties, component of a dendrimers, structure, different methods of synthesis of dendrimers, characterization and dendrimers based products and their use as pharmaceutical, therapeutic, diagnostic agent and their potential for applications in drug delivery such as carrier molecule, toxicity, current challenges, future prospect, conclusion. The review aims to emphasize on construction, characterization, drug delivery and possible application of dendrimers in various areas of research, technology and treatment.

KEY WORDS: Polymeric material, 3D structure, Hyper branched, High compatibility, Characterization, emphasize on construction.

INTRODUCTION

Several pharmacological active drugs report some difficulties such as poor water solubility, low half-half, lack of specificity, and biocompatibility issues. To overcome these disputes as well as improve the release characteristics, that is, products prepared in crystalline solid forms, amorphous forms, lipid-based formulations, polymer-drug conjugation. However, these technologies are associated with some stability and toxicity issues.[1]

Dendrimers have often been referred to as the "polymers of the 21st century". Dendrimers chemistry was first introduced in 1978 by fritz vogtle and co-workers. He synthesized the first "cascade molecule". In 1985, Donald A. Tomalia, synthesized the first family of dendrimers. At 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 well established one.

The word "dendrimers" originated from two Greek word- Dendron :- meaning tree,
Meros :- meaning part or segment.[2]

ADVANTAGES OF DENDRIMERS

Dendrimers show a structural uniformity and monodispersity.

- Dendrimers have a better/greater targeting efficiency due to the presence of reactive functional groups on the surface of dendrimer. Terminal groups may also be modified to reorganize specific receptors.
- The surface modification may allow designing dendrimers mimicking biological exo-receptors, substrates, inhibitors or cofactors.
- The similarity of dendrimers structure with IgM antibodies (pentamers radially distributed) suggest that they may be used to function as antibodies e.g. activation of macrophages, recognition, and high affinity to antigen.
- Dendrimers have the ability to deliver drug inside the cell or they may improve intracellular trafficking. [3]
- Dendrimers have s capability to entrap a variety of drugs having different types of functional groups in internal hollow core or by charge interactions.
- Dendrimers can be made stimuli responsive.
- Dendrimers have limited toxicity and immunogenicity but good biodegradability.
- They have better colloidal, biological and shelf-stability.
- They may be intrinsically anticancer agents in nature due to interferon, tumour necrosis factor including properties of acrylates. [4]

DISADVANTAGES OF DENDRIMERS

- Dendrimers show toxicity owing to the presence of a peripheral amine, guanidine, carboxylate, sulfonate, or phosphonate group
- Fast clearance from system circulation.
- Nonspecific drug delivery.
- Due to the open network of the dendrimer, they show poor control on drug release.
- In a covalently bound drug_dendrimer complex, there is an abrupt release of drug from the drug_dendrimer structure after exposure to the biological fluids due of interactive forces with the structure.[5]

IDEAL PROPERTIES OF DENDRIMERS

Many of the properties of dendrimers include :-

- Nanoscale sizes that have similar dimensions to important bio-building blocks for example, proteins, DNA.
- 2 Numbers of terminal surface groups (Z) suitable for bio-conjugation of drugs, signaling groups, targeting moieties or biocompatibility groups.
- Surfaces that may be designed with functional groups to augment or resist trans-cellular, epithelial or vascular bio-permeability.
- 4. An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties. Encapsulating in that void space reduces the drug toxicity and facilitates controlled release. [6]
- Positive biocompatibility patterns that are associated with lower generation anionic or neutral polar terminal surface groups as compared to higher generation neutral apolar and cationic surface groups.
- Non- or low-immunogenicity associated with most dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG).

- Surface groups that can be modified to optimize bio-distribution; receptor mediated targeting, therapy dosage or controlled release of drug from the interior space. [7]

STUCRURE

It is the hyper branching when going from the center of the dendrimers towards the periphery, resulting in homo structural layer between the focal point (branching points). That is a dendrimer having five focal points when going from the center to the periphery is denoted as the 5th generation dendrimers. Here we abbreviate this term to simply a G5- dendrimer. The core part of the dendrimer is some times denoted generation "zero", or in the terminology presented here "G0".

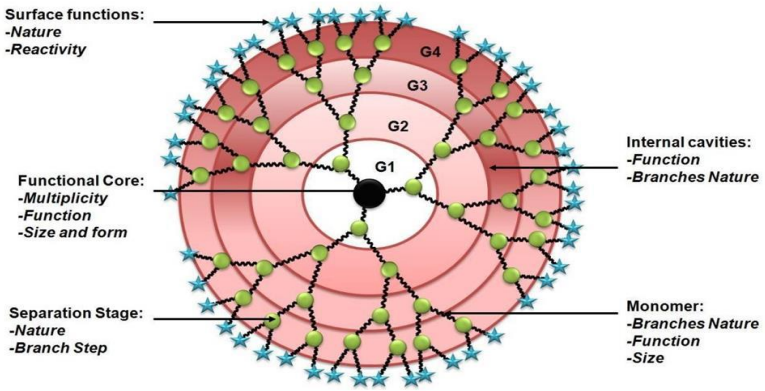


Fig 1 : structure of dendrimers

CLASSES OF DENDRIMER

(1) Radially Layered Poly (Amidoamine-Organosilicon) Dendrimers (Pamamos)

- In 1990, Dr. Petar Dvornic and his colleagues at MichiganMolecular Institute, discovered this uniquefirstcommercial silicon containing dendrimers. Consist ofhydrophilic, nucleophilic polyamidoamine (PAMAM)interiors and hydrophobic organosilicon (OS) exteriors.
- Excellent its networks regularity and ability to complexand encapsulate various guest species offerunprecedented potentials for new applications in nanolithography,electronics, photonics, chemical catalysis etc.and useful precursors for the preparation of honeycomblikenetworks with nanoscopic PAMAM and domains.
- synthesis method: Diverse and Convergent.
- Use: Chemical catalysis, nanolithography, electronics, and photonics are all precursors to honeycomb-like network preparations.
- E.g.: SARSOX

(2) Poly (Amidoamine) Dendrimers (Pamam)

- Synthesized by the divergent method, starting frominitiator core reagents like ammonia or ethylenediamine.
- When looking at the structure of the high-generation intwo-dimensions, star like pattern observed. They arecommercially available as methanol solutions and ingeneration G 0-10 with 5 different core type and 10 functional surface groups.
- Use: Computer toners, material science, and biomedicine.
- Eg : Pamamos Dendrimer:- DendritechTM [8]

(3) Poly (Propylene Imine) Dendrimers (Ppi)

- Poly (Propylene Imine) dendrimers (PPI) generally havingpoly-alkyl amines as end groups, and numerous tertiarytris-propylene amines present in interior portion. Itcommercially available up to G5, and wide applications inmaterial science as well as in biology.16 PPI dendrimersare available as AstramolTM.
- Synthesis process: Divergent.
- Use: Biology and materiology.
- Eg: Asramol by DSM.

(4) Chiral Dendrimers

- The chirality in these dendrimers is based upon theconstruction of constitutionally different but chemicallysimilar branches to chiral core. Their potential use aschiral hosts for enantiomeric resolutions and as chiralcatalysts for asymmetric synthesis.

- Use: Biomedical applications, chiral have for Enantiomeric goals and as chiral impetuses for unbalanced combination.
- Eg: pentaerythritol-derived chiral dendrimers .

(5) Crystalline Dendrimers

- A **Liquid** highly-branched oligomer or polymer of dendrite structure containing mesogenic groups that candisplay mesophase behaviour. They consist of mesogenic(liq. crystalline) monomers e.g. mesogen functionalizedcarbosilane dendrimers.
- Technique for Union:- Divergent.
- Use: Engineering and sciences.
- Eg : Mesogen-functionalized carbosilane dendrimers .

(6) Tecto Dendrimer

- Tecto Dendrimer are composed of a core dendrimer,perform varied functions ranging from diseased cellrecognition, diagnosis of disease state drug delivery,reporting location to reporting outcomes of therapy.
- Structure: It had multiple dendrimers at its periphery in addition to a central dendrimer.
- Synthesis process: Diverse
- Uses: Diseased state drug delivery diagnosis, diseased cell recognition, and reporting location to therapy outcome
- Eg: Mercapto, Starburst®, and Stratus® CS Acute Care TM

(7) Hybrid Dendrimers

- Hybrid dendrimers are hybrids (block or graft polymers)of dendritic and linear polymers. Obtained by completemonofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, providestructurally diverse lamellar, columnar, and cubic selforganizedlattices that are less readily available fromother modified dendritic structures.
- Synthesis process: Divergent.
- Use: Nanophotonics, biomedical electronics, and sensing technologies,
- example: Polysilsesquioxanes are a hybrid dendritic linear polymer

(8) Multilingual Dendrimers

- Multilingual Dendrimers contains multiple copies of aparticular functional group on the surface.

(9) Micellar Dendrimers

- Micellar dendrimers are unimolecular water solublehyper branched polyphenylenes micelles **.**
- Synthesis Process: Diverse
- Uses: applications in biology and medicine, drug delivery, and imaging agent.
- Eg : Magnevist® NX-200, beclomethazone dipropionate:

(10) Amphiphilic Dendrimers

- Amphiphilic dendrimers are built with two segregatedsites of chain end, one half is electron withdrawing andthe other half is electron donating.
- Technique for Amalgamation: Divergent.
- Use: Transfection of cells and genes, use as a polar component, and structure- directiMicellar Dendrime Ex :- SuperFect, Hydraamphiphiles, and Bolaamphiphiles

(11) Peptide Dendrimers

- Multiple Antigen Peptide dendrimers is a dendron-likemolecular construct, use in biological applications, *e.g.*vaccine and diagnostic research. Peptide dendrimers canbe used as drug delivery, contrast agents for magneticresonance imaging (MRI), magnetic resonanceangiography (MRA), fluorogenic imaging and sero diagnosis.
- Synthesis Process: Convergent.
- Use: in the study of diagnostics and vaccines. Applications in biology.
- Eg : VivaGel

***(*12) Frechet-Type Dendrimers**

- Frechet-Type Dendrimers have carboxylic acid groups assurface groups, serving as a good anchoring point forfurther surface functionalisation, and as polar surfacegroups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media.
- Method of Synthesis: Use in Convergence: Drug delivery, purifiers, organic synthesis, drug carrier, detecting agent
- Eg : Dendron azides, PriostarTM

(13) Simple Dendrime

They have simple monomer units e.g.poly (amidoamine) dendrimers composed of poly (amidoamine) segments named as “starburst” dendrimers. Tomalia 1st reported the synthesis of starburst dendrimers in 1985.

(14) Triazine Dendrimers

- 1,3,5-Triazine is an important moiety, which can be incorporated in the dendrimer structure because of some unique properties, namely, biological activities, high stability on functionalization, easy Triazine-based dendrimers have also been found to show antibacterial activity with good chemical stability, less volatility, and nonirritant to the skin. [9]

TYPES OF DENDRIMERS

Drug-Loaded Dendrimer As Nanovehicles

These units further terminate as leaves, which can be related to surface functional moieties. Increasing the number of branches around the core creates crowding, hence shielding the core from the outside environment.

Simple Dendrimers In Gene Transfection

An ideal DNA vector, it should have following characteristics such as target specificity, high transfection efficiency, easily biodegradable, stability, less potential
to be toxic or immunogenic, easy design, and synthesis.

Pegylated Dendrimers In Cancer Therapy

PEGylation simply means the conjugation of PEG to the dendritic scaffold. PEGylated dendrimers are more efficient than others in terms of drug loading, targeting, and solubilization (due to attached PEG chains).

MECHANISMS OF DRUG DELIVERY

- **Simple encapsulation :** it directly encapsulates guest molecules intomacromolecules interior .
- **Electrostatic interaction :** surface functional groups enhance solubility of hydrophobic drugs by electrostatic interaction e.g. Ibuprofen,ketoprofen ,indomethacin.
- **Covalent conjugation :** the drugs is covalently bound to denbdrimers & its cleavage occurs via chemical or enzymatic cleavage of hydrolytically labile bonds. It allow tissue targeting & controlled delivery as drug-dendrimers conjugate diffuse slower thanthe free.

TECHNOLOGY OF DENDRIMERS PRODUCTION

METHOD OF SYNTHESIS

(1) Divergent method.
(2) Convergent method .
(3) Hypercores and branced monomers method.
(4) Double exponential and mixed growth.
(5) Other accelerated growth technique.

1) DIVERGENT METHOD

Dendrimers starts from the center core and extents towards the i.e diverging into space. It is two step process. Activation of functional surface groups and Addition of branching monomers units. Divergent approach is successful for the production of large quantities of dendrimers. It causes some difficulties in the purification of the final product.

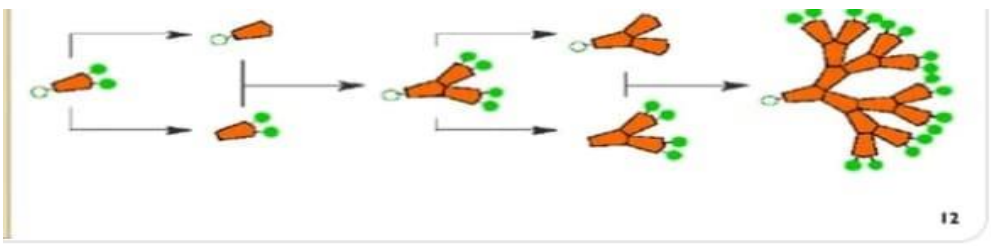


Fig 2: synthesis of dendrimers

(2) CONVERGENT METHOD

Dendrimers starting from the end groups and progessing inwards. When the growing wedges are enough large, attached to a suitable core to give a complete dendrimer. The convergent methodology also suffers from lwo yields in the synthesis of large structures.

Advantages:-Relatively easy to purify the desired product.

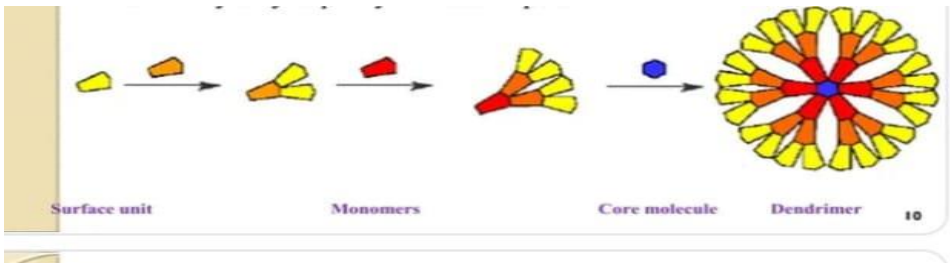


Fig 3: synthesis of dendrimers by convergent method

(3) HYPERCORES AND BRANCED MONOMERS METHOD.

Frechet group continued their efforts on research of hyper core and branced monomer. This method is involves the preassembly of oligomeric species, which can then be linked together to give dendrimer. This monomer allow the to design synthetic strategies that are more convergent in classical synthetic sense of word.

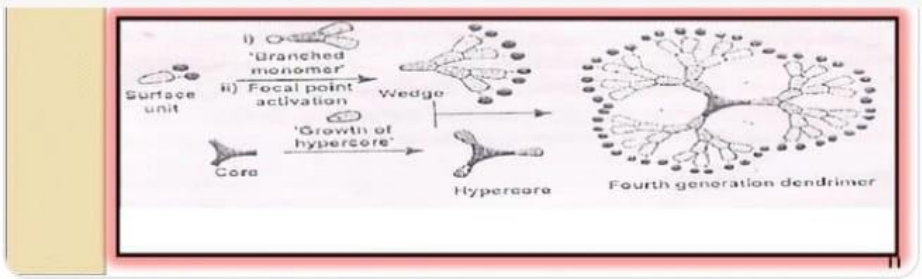
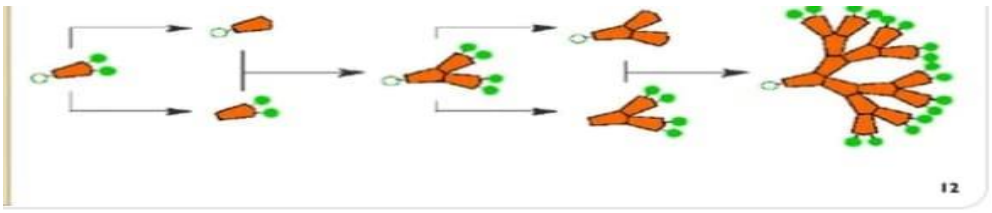


Fig 4: synthesis of dendrimers by branced monomers method

(4) DOUBLE EXPONENTIAL AND MIXED GROWTH

Double expontial growth, similar to rapid technique for linear polymer involves and AB_2 monomer with orthogonal protecting groups or the A and B functionalities, This approach allow the prepration of monomers for both convergent and divergent growth from a single staring material. These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth procces again.



(5) OTHER ACCELERATED GROWTH TECHNIQUE.

In this approach two different monomer are used so as to avoid the need of an activation state between growth steps. The two monmeric units are AB2 & CD2 where A&D reacts to form bond under required

conditions while B&C are stable, where B&C reacts to form bond while A&D remain stable. In this technique the hindrance likely to be experienced is that difficulty of finding a set of reactions, which confirm to above criteria. This first synthesized dendrimer was **polyamidoamines (PAMAMs)**,They are also known as ***starbust dendrimers***.[10]

APPLICATION

1. The cancer patient is injected with boron attached to dendrimer.
2. It migrates to cancerous cells.
3. Then irradiate with neutral beam of low energy neutrons.
4. This generate alpha particles which destroy tumour cell.

Fig 5: Application of dendrimers

Future prospective

Dendrimer future prospects include the development of dendrimers clusters, in which multiple dendrimers are bound together through physical or chemical forces to assemble a multifunctional therapeutic system that incorporates the anticancer drugs, targeting ligands, and imaging agents. Dendrimer future prospects: The difficulty of synthesizing the desired systems in large quantities at clinical grade purity for clinical trials and regulatory hurdles that require detailed characterization of the polymeric carriers along with the linkages and the incorporated drug make their application in cancer therapies with defined dosage regimens still not acceptable, despite their effectiveness.

DENDRIMER BASED PRODUCTS

Several dendrimer grounded products have formerly been approved by the FDA and some in Phase II clinical trials.
Various dendrimer based products are

- Alert ticket for Anthrax Detection
- Priofect ™, Priostar ™ and Starburst for targeted Diagnostic, remedial delivery for cancer cells
- SuperFect for Gene Transfection
- Stratus CS for Cardiac Marker
- Vivagel for precluding HIV [11]

COCLUSION

Dendrimers are macromolecular nanoparticles used in drug synthesis. Each dendrimer has unique characteristics that make it a potential candidate for a variety of applications.

Dendrimers have numerous applications due to their structural versatility, which makes them less cytotoxic and improves the drug Polyethylene glycol's (PEG) stability.

They can be utilized in a variety of fields, including immunology and biopharmacy; the multi-step amalgamation actually Requires incredible exertion.

When it comes to the formulation and development of a drug entity, physicochemical properties, such as solubility, must be taken into account.

However, this hyperbranched three-dimensional carrier has demonstrated its ability to solubilize and carry a variety of hydrophobic drug molecules with success.

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