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DENDRIMER- A NOVEL TECHNIQUE FOR DRUG DELIVERY

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ABSTRACT

Introduction: Dendrimers are a novel class of synthetic macromolecules having highly branched, three dimensional, nanoscale structures with very low poly dispersity and high functionality. The structure of these materials has a great impact on their physical and chemical properties. These unique features have made their application in nanotechnology, pharmaceutical and medical chemistry particularly attractive. As a result of their unique behavior, dendrimers are suitable for a wide range of biomedical and industrial applications. **Structure:** These carriers have well defined size, shape, molecular weight and monodispersity, which make the dendrimers a suitable carrier in drug delivery application. Dendrimers are uni-molecular micelle in nature and due to this enhances the solubility of poorly soluble drugs. These polymers have also successfully proved themselves as useful additives in different routes of drug administration because they can render drugs of greater water solubility, bioavailability and biocompatibility. **Synthesis:** Dendrimers possess empty internal cavities and open conformations, which make it possible to encapsulate hydrophobic drug molecules. In addition, they have a much higher surface functional group density when compared with conventional macromolecules. **Conclusion:** This review article focuses on the various aspects of dendrimers including structure, properties, and types of dendrimers, preparation methods and their applications in pharmaceutical as well as non-pharmaceutical field.

KEYWORDS: Bioavailability, Divergent, Convergent, PAMAM, PAMAMOS.

INTRODUCTION

A strong demand on high quality polymeric products inclines the polymer scientists to produce their polymers with novel and innovative ideas. Polymer chemistry and technology

have traditionally focused on linear polymers, which are widely in use. Linear macromolecules only occasionally contain some smaller or longer branches.[1]

In the recent past it has been found that the properties of highly branched macro-molecules can be very different from conventional polymers. The structure of these materials has also a great impact on their applications. A strong demand on high quality polymeric products inclines the polymer scientists to produce their polymers with novel and innovative ideas.

Dendritic architecture is undoubtedly one of the most pervasive topologies observed universally throughout biological systems. These patterns are found at virtually all dimensional length scales. They appear in many diverse prototypes including those that can be measured in meter, in circulatory topologies in the human anatomy that are found in mm and cm, or in cerebral neurons in μm.[1-2]

The term dendrimer originates from Greek word **'Dendron'** meaning a tree. The synonym for Dendrimer is **'Arborols'** (from latin word 'arbor') also meaning a tree and **'Cascade molecule'** but 'dendrimer' is the best established one.. These initially small hyper-branched molecules were the basis for polypropylene imine (PPI) dendrimers. Dendrimers are repetitively branched molecules roughly spherical large molecules and possess well defined chemical structures, consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped having diameters in the 2 to 10 nm range.Dedrimer having very low poly-dispersity and high functionality. A dendron usually contains a single chemically addressable group called the focal point (branching points).[3]

Dendrimers provide a route to create very well defined nano-structures suitable for drug solubilization applications, delivery of oligonucleotide, targeting drug at specific receptor site, and ability to act as carrier for the development of drug delivery system. Dendrimers are being considered as additives in several routes of administration, including intravenous, oral, transdermal, pulmonary and ocular.[4]

Terms & Nomenclature in Dendrimer Chemistry

Dendrimer chemistry, as other specialized research fields, has its own terms and abbreviations. The evolution of three major macromolecular architecture, namely: linear (class I), cross-linked (bridged; class II) and branched types (class III). These three architectural classes are recognized as traditional synthetic polymers. In all these classes,

structures or architectures are produced by largely statistical polymerization processes, rather than exact distribution processes.[5]

Structure

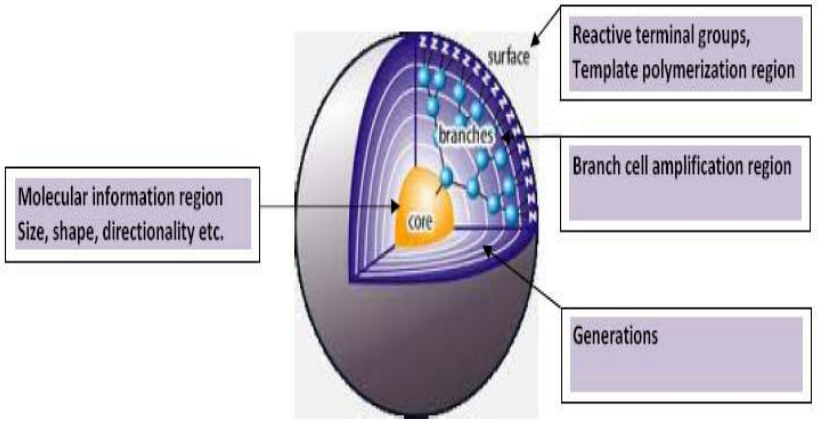

Fig. 1: The Dendrimer Structure.

Dendrimers are built from a starting atom, such as nitrogen, after a repeating series of chemical reactions, carbon and other elements was added into it; produce a spherical branching structure. As the process repeats, result is a spherical macromolecular structure.[1]

Dendrimers possess three distinguished architectural components, namely a central core which is either a single atom or an atomic group. Generation in which branches emanating from the core composed of repeating units, which is radially in position and many terminal functional group generally located in the exterior of the macromolecule.[6-7]

Four main components are present in the dendrimer structure like Generation number is the number of focal points when going from the core towards the dendrimer surface, if dendrimer when going from the centre to the periphery having five focal points, is denoted as the 5^{th} generation dendrimer.[7]

Between the focal points and the generation space, the homo-structural spatial segment is present that is Shell. The space between the last outer branching point and the surface known as outer shell, consists of a varying number of Pincers created by the last focal point before reaching the dendrimer surface.[8]

End group is also known as terminal group or surface group of the dendrimer, if dendrimers having amine end-groups are termed ―amino-terminated dendrimers.[9]

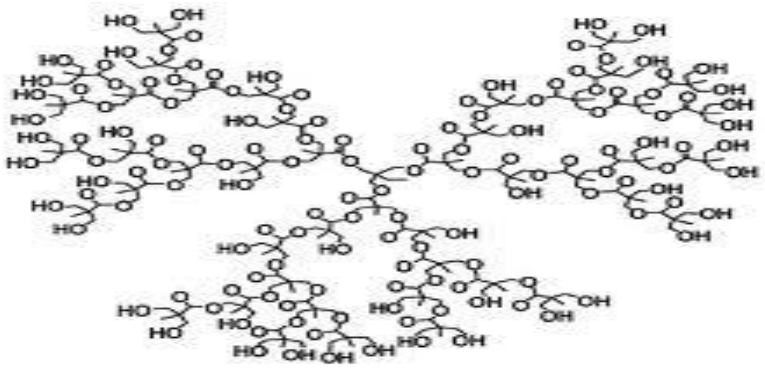

Fig. 2: Structure of dendrimers.

Snthesis of Dendrimers

The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis.[9]

- Divergent growth method
- Convergent growth method
- Hyper cores and branched monomers growth
- Double exponential growth

First two are the Main two methods for synthesis of dendrimers.

(a) Divergent synthesis of dendrimer: In this method growth of Dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained. By this approach the first synthesized Dendrimers were polyamidoamines (PAMAM), also known as starbust Dendrimers**.**[10]

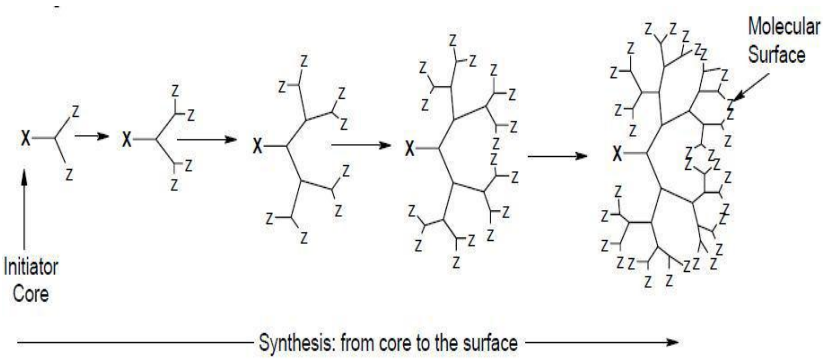

Fig. (a): Divergent synthesis of dendrimer.[9]

Merit

- Large quantity of dendrimer produced by this method.

Demerit

- To prevent problem during synthesis large quantity of reagent required.
- Product purification is very tedious task.

(b) Convergent Dendrimer Growth

Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.[11]

An advantage of convergent growth over divergent growth is that purification Is done after each step whereas in divergent methodsince the reactant and product remains same it is difficult to purify by chromatographic technique.

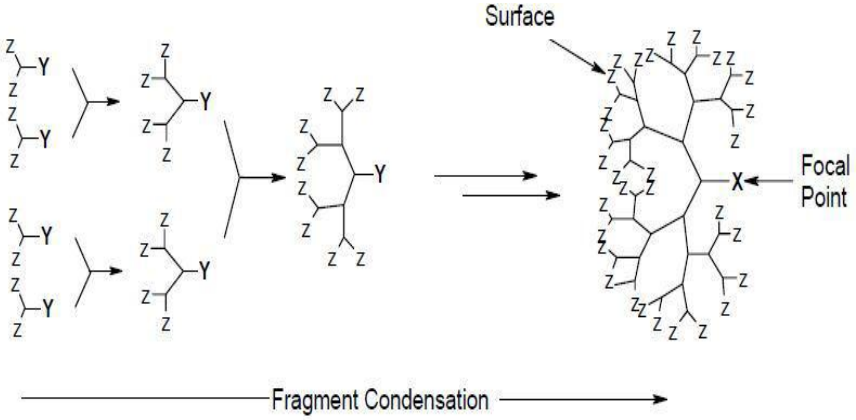

Fig. (b): Convergent synthesis of dendrimer.[9]

Merit

- Defects in the final structure are less. Product easily purified.

Demerit

- Due to steric hindrance higher generation dendrimer cannot be formed.

(c) Hypercores' and 'Branched Monomers growth

Linkage of the oligomeric species in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation Dendrimers.[12]

Merit

- Fewer steps, Higher yields.

(d) Double Exponential' or 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.

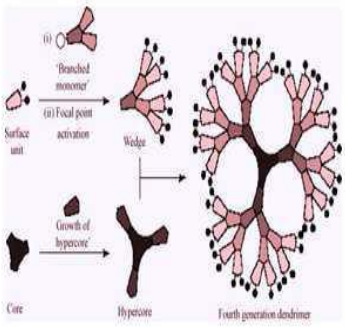

Fig.4. 'Hypercores' and 'Branched Monomers growth

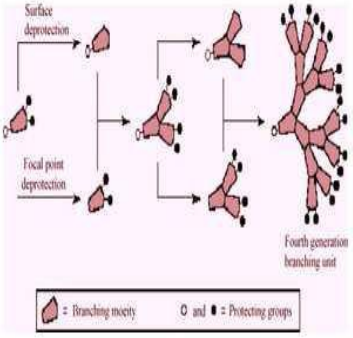

Fig 5. 'Double Exponential' growth

OBJECTIVES

- Improve the pharmacokinetic and pharmacodynamics properties of a drug so that there is also an accretion in bioavailability.
- Achieve the controlled and targeted release of drug restricted to the area desired.[33]

Advantages

Advantages of Dendrimers

- Dendrimers offers various advantages over other polymers:
- Dendrimers have nano-scopic particle size range from 1 - 100 nm, which makes them less susceptible for reticulum endothelium uptake.

- They have lower poly-dispersity index, due to stringent control during synthesis. As the density of branches increases the outer most branches arrange themselves surrounding a lower density core in the form of spheres and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.
- Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.
- Dendrimers can be modified as stimuli responsive to release drug.
- Dendrimers might show an enhanced permeability and retention effect which allows them to target tumour cells more effectively than small molecules.
- They can be synthesized and designed for specific applications. Due to their feasible topology, functionality and dimensions, they are ideal drug delivery systems; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.[35]

Disadvantages

1. It is not suitable for oral drug delivery because drug– dendrimer complex not cross gut wall.
2. Drug–dendrimer construct is considered as new chemical entity so that clinical testing for new construct required.[35]

Types of Dendrimers[18-30]

- PAMAM Dendrimer
- PAMAMOS Dendrimer
- PPI Dendrimer
- POPAM
- Tecto Dendrimer
- Chiral Dendrimers
- Hybrid Dendrimers
- Liquid Crystalline Polymers
- Amphiphilic Dendrimers
- Micellar Dendrimers
- Multiple Antigen Peptide Dendrimers
- Frechet-Type Dendrimers

- Multilingual Dendrimers

➢ **Pamam Dendrimer**

Poly (amidoamine) dendrimers / starburst Dendrimer

Method of synthesis: Divergent starting from ammonia or ethylenediamine initiator core reagents. PAMAM dendrimers are commercially available as methanol solutions. Starburst name to PAMAM dendrimer due to the starlike pattern observed when looking at the structure of the high generation dendrimers of this type in two dimensions.[13-18]

Use

- Material Science
- Biomedicine Computer toners.

Eg: DendritechTM

➢ **Pamamos Dendrimer**

Radially layered poly (amido amine organosilicon) Dendrimers

In 1990, Dr. Petar Dvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers.[19]

Structure

End group: Hydrophobic organosilicon (OS)

Interior part: Hydrophilic, nucleophilic polyamidoamine

Method of synthesis: Convergent and Divergent.

Use

- Nano-lithography
- Electronics
- Photonics
- Chemical catalysis
- Precursor for honeycomb like network preparations.

Eg: SARSOX

➢ **PPI Dendrimer**

Poly-Propylene Imines/DAB/POPAM

Is the oldest known dendrimer type developed initially by Vogtle

Structure

End group: Primary amines.

Interior part: Numerous tertiary trispropylene amines. PPI dendrimers are commercially available up to G5.

POPAM

POPAM is alternative name to PPI. It stands for Poly (Propylene Amine).

It also called as DAB-dendrimers where DAB refers to the core structure, which is usually based on Diamino butane.[20]

Method of synthesis. : Divergent

Use: Material science and biology.

Eg: Asramol by DSM

➢ **Tecto Dendrimer**

Structure: It composed of a core dendrimer with multiple dendrimers at its periphery.

Method of synthesis: Divergent

Use

- Diseased cell recognition
- Diseased state drug delivery diagnosis
- Reporting location to outcome of therapy.

Eg: Stratus® CS Acute Care TM, Starburst®, Mercapto

➢ **Chiral Dendrimer**

Structure: Chilarity is based on construction of constitutionally different but chemically similar branches to a chiral core.[19-20]

Method of synthesis: Convergent.

Use

- Biomedical applications
- Chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis.

Eg: chiral dendrimers derived from pentaerythritol.

➢ **Hybrid Dendrimer**

Structure: These are hybrids (block or graft polymers) of dendritic and linear polymers obtained by complete mono functionalization of the peripheral amines of a "zero-generation". Polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic self-organized lattices that are less readily available from other modified dendritic structures.[21-23]

Method of synthesis: Divergent.

Use

- Bio-medicals
- Molecular electronics
- Nano-photonics
- Sensing

Eg: Hybrid dendritic linear polymer, Polysilsesquioxanes.

➢ **Liquid Crystalline Dendrimer**

Structure: A highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour. They consist of mesogenic (liq. crystalline) monomers.[23]

Method of Synthesis

Divergent.

Use: Science and Engineering.

Eg: Mesogen functionalized carbosilane dendrimers

➢ **Amphiphil Dendrimer**

Structure: Unsymmetical globular dendrimers built with two segregated sites of chain end. One half is electron donating and the other half is electron withdrawing.[24]

Method of Synthesis: Divergent.

Use

- Structure-directing agent
- Use as polar part, cell and gene transfection.

Eg: SuperFect, Hydraamphiphiles and bola-amphiphiles

➢ **Micellar Dendrimer**

Structure: These are uni-molecular micelles of water soluble hyper-branched polyphenylenes.

Method of Synthesis: Divergent

Use

- Biological and medical applications
- Drug delivery
- Imaging agent.

Eg: Beclomethazone dipropionate, NX-200, Magnevist®

➢ **Multiple Antigen Peptide Dendrimer**

This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications.[25]

Structure: It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points.[26-28]

Method of Synthesis: Convergent.

Use

- In vaccines and diagnostic research
- Biological applications.

Eg: VivaGel

Frechet Type Dendrimer

Structure: Dendrimes having carboxylic acid groups as surface groups and containing poly-benzyl ether hyperbranched skeleton.[27]

Method of Synthesis: Convergent

Use

- Drug carrier
- Purifiers
- Organic synthesis
- Detecting agent,
- Drug delivery.

Eg: Dendron azides, PriostarTM

Properties of Dendrimer

Monodispersity

Dendrimer are monodisperse having same size. Dendrimer synthesis is specifically controlled which reduces size variation unlike linear molecule synthesis produces random structure and high size variation. Dendrimer synthesized from convergent method having high monodispersity than other method. Most of structural defect occur during formation of high generation dendrimer because of incomplete reaction, steric hinderance problem.[29-30]

Technique of characterisation for Monodispersity

- Mass spectroscopy
- Size exclusion chromatography
- High performance liquid chromatography
- Transmission electron microscopy
- Gel Electrophoresis

Solubility

Functional group present on surface decide solubility of dendrimer. Hydrophilic group on surface is soluble in polar solvent like water. Hydrophobic group on surface soluble in non-aqueous solvent. Internal cavity carries hydrophobic drug and improves solubility. In a solubility test with tetrahydrofuran as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester.[31]

Size and Shape

Size of Dendrimer is in nanometer. Due to less particle size not only dendrimer easily cross the cell membrane but also clearance from body is reduced. Dendrimers show some significantly improved physical and chemical properties because of their molecular architecture, as compared to traditional linear polymers. Shape of dendrimer depend upon generation of dendrimer.

Lower generation

Open planer elliptical shape.

Higher generation

Compact spherical shape.

Rheological Property

In solution linear chains exist as flexible coils, in contrast dendrimers form a tightly packed ball which influences its rheological properties. Dendrimer having less viscosity than linear polymer. As molecular mass increases intrinsic viscosity increases upto 4th generation dendrimer then decreases.[32]

Crystallinity

Dendrimer are non-crystalline and amorphous materials

Immunogenicity

Dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) they become nonimmunogenic or less immunogenic.

Cytotoxicity

Cytotoxicity of dendrimer depend upon core of dendrimer but it also affected by functional group present on surface of dendrimer having amino (-NH2) group at surface shows cytotoxic property but this also depend upon generation of dendrimer and concentration. Higher generation dendrimers being the most toxic.[32]

Factors affecting dendrimers

Table 1: Factors affecting Dendrimer properties.

S. No	Factor	Level	Effect
1	**Effect of pH**	Low	-Structural behaviour of PAMAM dendrimers is depended upon pH. -At low pH (< 4) the interior is getting increasingly **hollow.** -Repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior increases at high generation.
		Neutral	-At neutral pH, back-folding occurs which may be a consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines.
		High	-At higher pH (pH>10) the dendrimer contract as the charge of the molecule becomes neutral, acquiring a more spherical (globular) structure, where the repulsive forces between the dendrimer arms and between the surface groups reaches minimum.
2	**Effect of Salt**	High	-High concentration of salt have a strong effect on charged PPI dendrimers. Favours a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor solvation.
		Low	-The repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure.
3	**Effect of Solvent**		-The solvation power of any solvent to solvate the dendrimer is a very important parameter. -Dendrimers of all generations generally exhibit a larger extent of back-folding with decreasing solvent quality. -The dendrimer arms induce a higher molecular density on the dendrimer surface. -NMR studies performed on PPI dendrimers concluded that a nonpolar Solvent like benzene, poorly solvates the dendrimers favouring intramolecular interactions between the dendrimer segments and back folding.
4	**Effect of Concentration of Dendrimer**		-Small angle X-ray scattering (SAXS) experiments performed on PPI dendrimers (G4, G5) in a polar solvent like methanol show that the molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted. -This molecular contraction may minimize the repulsive forces between the dendrimer molecules and increase the ability of the dendrimers to exhibit a more tight intermolecular packing.

APPLICATION OF DENDRIMER

Pharmaceutical application

Dendrimer in ocular drug delivery: Ideal ocular drug-delivery systems should be non-irritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery.[20]

Dendrimers in 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 %.[20]

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. PAMAM dendrimer complex with NSAIDs could be improving the drug permeation through the skin as penetration enhancers.[20]

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. Remarkably, the 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.[20]

Dendrimers for controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construct involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5- fluorouracil. Encapsulation of 5-fluorouracil into G=4 increase in the cytotoxicity and permeation of dendrimers.[28]

Dendrimers in 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 PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. A third-generation dendritic uni-molecular micelle with indomethacin entrapped as model drug gives slow and 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.[24]

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. The use of dendrimers as gene transfection agents and drug-delivery devices have been extensively reviewed part. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.[17]

Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its Uni-molecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behavior.[15]

Cellular delivery using dendrimer carrier: Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug, suggesting 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.[20]

Therapeutic application

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.[25]

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 multivalent.[18]

Diagnostic application

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.[27]

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.[27]

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.[32]

CONCLUSION

Dendrimers are characterized by individual features that make them hopeful candidates for a lot of applications. Dendrimers are highly defined artificial macromolecules, which are characterized by a combination of a high number of functional groups and a compact molecular structure. A rapid increase of importance in the chemistry of dendrimers has been observed since the first dendrimers were prepared. Work was established to determine the methods of preparing and investigating the properties of the novel class of macro and micromolecules. In spite of the two decades since the finding of dendrimers, the multi-step synthesis still requires great effort.

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