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Review Article

A COMPREHENSIVE REVIEW ON DENDRIMERS

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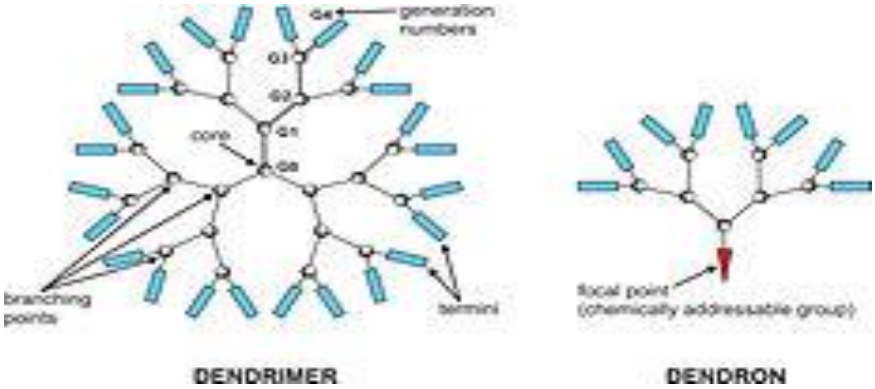
ABSTRACT

Dendrimers also known as arborols are nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches**.** These are synthetic 3-dimensional macromolecules prepared in a stepwise way from simple branched monomer units, whose nature and functionality can be easily controlled and varied. Their structure results in previously unknown or improved physical and chemical properties as compared to the common linear polymers. Dendrimers are now one of the most important nanometer-scale building blocks for the construction of nanoscale systems, molecular devices, advanced drug-delivery systems, *etc.* This review gives concise information about dendrimers' physico-chemical properties, synthetic strategies and their possible use in various areas of research, technology and treatment.

Key words: Dendrimers, Convergent synthesis, divergent synthesis, drug delivery, sensor technology.

INTRODUCTION

Dendrimers are repetitively branched molecules. A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. A dendron usually contains a single chemically addressable group called the focal point. The difference between Dendron's and dendrimers is illustrated in figure but the terms are typically encountered interchangeably. The first dendrimers were made by divergent synthesis approaches by Fritz Vögtle in 1978, R.G. Den kewalter at Allied Corporation in 1981,Donal d Tomalia at Dow Chemical in 1983 and in 1985, and by George Newkome in 1985. In 1990 a convergent synthetic approach was introduced by Jean Fréchet.



STRUCTURE OF DENDRIMER

Dendrimers are also known as arborols or cascade molecules 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. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin.

Dendrimers possess three architectural components namely

- An initiator core.
- Interior layers (generations) composed of repeating units, radically attached to the interior core.
- Exterior (terminal functionality) attached to the outermost interior generations.

COMPONENTS OF A DENDRIMER STRUCTURE

Branching units:

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.

For instance, 5th generation polypropylene imine is abbreviated to a "G5-PPI-dendrimer'.

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".

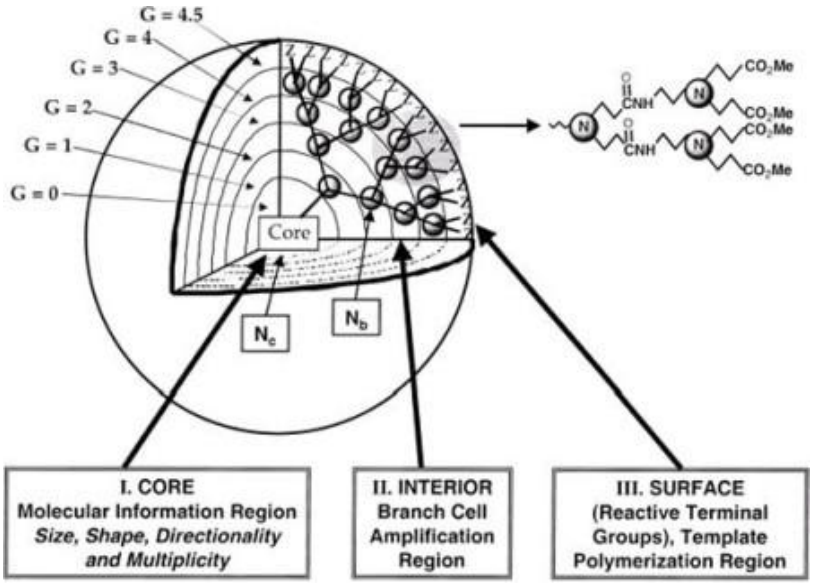
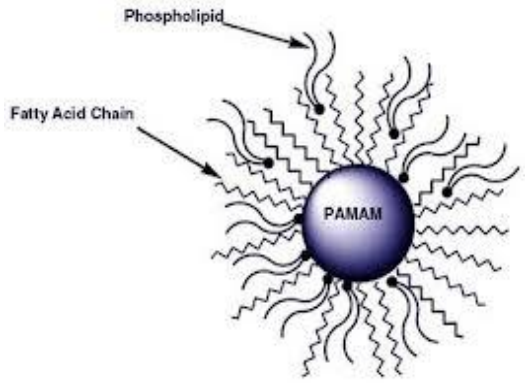


Fig.2.Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface

TYPES OF DENDRIMERS

1. PAMAM Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10 with a molecular weight of over 9, 30,000 g/mol. PAMAM dendrimers are commercially available, usually as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers.



2. PAMAMOS Dendrimer

Radially layered 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 domains.

3. PPI Dendrimer

These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consist of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology.

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. Many dendrimer syntheses rely upon traditional reactions, such as the Michael reaction or the Williamson ether synthesis whilst others involve the use of modern techniques and chemistry.

Divergent Dendrimer synthesis:

The synthetic methodology employed in the early dendrimer syntheses came to be known as the divergent approach. This name comes from the way in which the dendrimer grows outwards from the core, diverging into space. Starting from a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers. The two steps can be repeated. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is doubled. Divergently grown dendrimers are virtually

impossible to isolate pure from their side products. The synthetic chemist must rely on extremely efficient reactions in order to ensure low polydispersities. The first synthesized dendrimers were polyamidoamines (PAMAMs).They are also known as starburst dendrimers.

Convergent Dendrimer synthesis:

The convergent approach was developed as a response to the weaknesses of divergent synthesis. 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. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer.

. The convergent growth method has several advantages:

- Relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised.
- Possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecules.
- Approach does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.

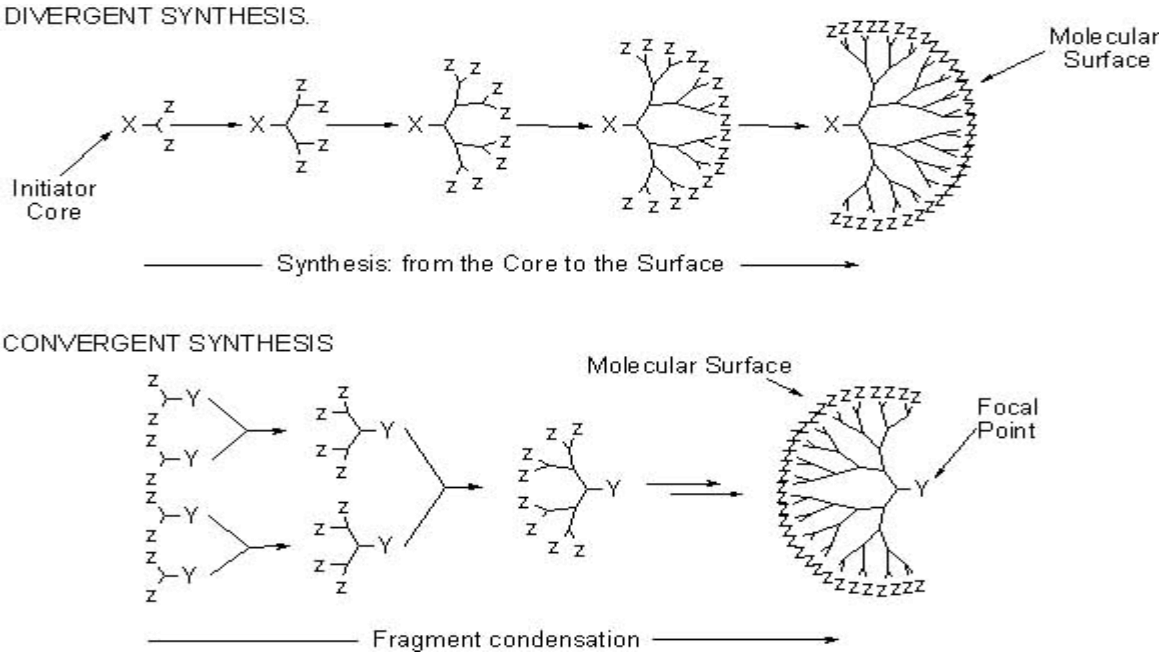


Fig.3.Convergent & divergent arborol Synthesis

Double Exponential Growth:

- The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' 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. The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.
- The double exponential methodology provides a means whereby a dendritic fragment can be extended in either the convergent or the divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings.

PHARMACEUTICAL APPLICATIONS

Dendrimers as novel drug delivery system:

Approaches for delivering unaltered natural products using polymeric carriers is of widespread interest, dendrimers have been explored for the encapsulation of hydrophobic compounds and for the delivery of anticancer drugs. The physical characteristics of dendrimers, including their monodispersity, water solubility, encapsulation ability, and large number of functionalizable peripheral groups, make these macromolecules appropriate candidates for evaluation as drug delivery vehicles. There are three methods for using dendrimers in drug delivery: first, the drug is covalently attached to the periphery of the dendrimer to form dendrimer prodrugs, second the drug is coordinated to the outer functional groups via ionic interactions, or third the dendrimer acts as a unimolecular micelle by encapsulating a pharmaceutical through the formation of a dendrimer-drug supramolecular assembly. The use of dendrimers as drug carriers by encapsulating hydrophobic drugs is a potential method for delivering highly active pharmaceutical compounds that may not be in clinical use due to their limited water solubility and resulting suboptimal pharmacokinetics. Dendrimers have been widely explored for controlled delivery of antiretroviral bioactives. The inherent antiretroviral activity of dendrimers enhances their efficacy as carriers for antiretroviral drugs. The dendrimer enhances both the uptake and retention of compounds within cancer cells, a finding that was not anticipated at the onset of studies. The encapsulation increases with dendrimer generation and this method may be useful to entrap drugs with a relatively high therapeutic dose. Studies based on this dendritic polymer

also open up new avenues of research into the further development of drug-dendrimer complexes specific for a cancer and/or targeted organ system. These encouraging results provide further impetus to design, synthesize, and evaluate dendritic polymers for use in basic drug delivery studies and eventually in the clinic.

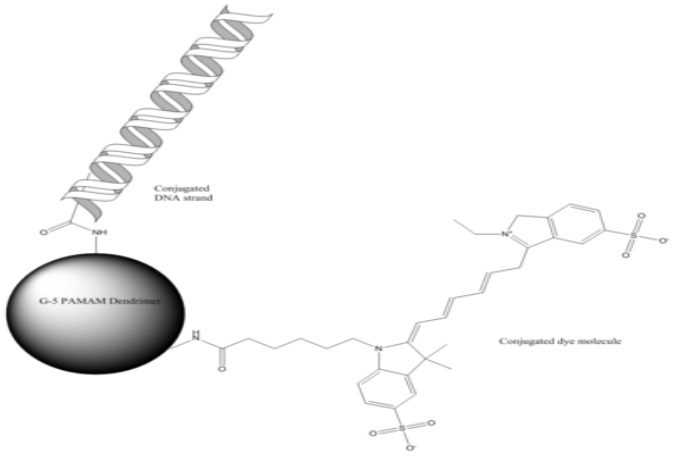
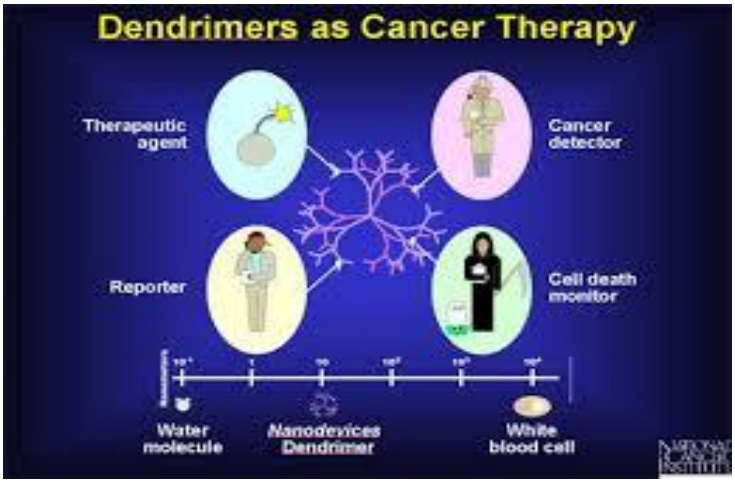


Fig.4.Depicting the dendrimer in conjugation with dye molecule

Delivery of Antineoplastic drugs by Dendrimers:

The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h).In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. Combined, these factors lead to the selective accumulation of macromolecules in tumor tissue – a phenomenon termed the 'Enhanced Permeation and Retention' (EPR) effect. Therefore, the anticancer drug doxorubicin was covalently bound to this carrier via an acid-labile hydrazone linkage. The cytotoxicity of doxorubicin was significantly reduced (80–98%), and the drug was successfully taken up by several cancer cell lines.



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 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).In earlier studies, it was found that PAMAM dendrimers covalently modified with naphthyl sulfonate residues on the surface also exhibited antiviral activity against HIV. This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities. PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be potent antibacterial biocides against Gram positive and Gram negative bacteria. Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications.

***Dendrimers in Photodynamic Therapy* (PDT)**

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes .Photos ensitive dyes have been incorporated into dendrimers and utilized in PDT devices. 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.

Dendrimers in Sensor technology:

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using poly (propylene imines), cadmium- sulphide/ polypropylenimine Tetrahexacontaamine dendrimer composites to detect fluorescence signal quenching, Poly (propylenamine) first and second generation dendrimers for metal cation photo detection.Research in this field is vast and ongoing due to the potential for multiple detection and binding Sites in dendritic structures.

Dendrimers as Blood substitutes:

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.

CONCLUSION

Due to their unique architecture dendrimers have improved physico-chemical properties. These have well defined size shape molecular weight monodispersity and they are unimolecular in nature. These properties make the dendrimers a smart choice for drug delivery applications and enhance the solubility of poorly water soluble drugs. Also further research has to be done to understand the absorption, bioavailability, formulation aspects, and uptake mechanisms by biological membranes and *invivo* stability.

REFERENCES

1. Tomalia D.A, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder and Smith P, "A New Class of Polymers: Starburst-Dendritic Macromolecules", Polym. J., 17(1), 117-132, 1985.
2. Pushkar S, Philip A, Pathak K and Pathak D, "Dendrimers: Nanotechnology Derived Novel Polymers in Drug Delivery", Indian J. Pharm. Educ. Res., 40 (3), 153-158, 2006.
3. D. Astruc, E. Boisselier, C. Ornelas (2010). "Dendrimers Designed for Functions: From Physical, Photophysical, and Supramolecular Properties to Applications in Sensing, Catalysis, Molecular Electronics, and Nanomedicine". *Chem. Rev.* 110 (4): 1857–1959.
4. Vögtle, Fritz / Richardt, Gabriele / Werner, Nicole *Dendrimer Chemistry Concepts, Syntheses, Properties, Applications* 2009 ISBN 3-527-32066-0.
5. Pushkar S, Philip A, Pathak K,Pathak D "Dendrimers: Nanotechnology Derived Novel Polymers in Drug Delivery", Indian J. Pharm. Educ. Res., 40 (3), 153-158, 2006.
6. Sakthivel T and Florence A.T, "Adsorption of Amphipathic Dendrons Polystyrene Nano particles", Int. J. Pharm., 254, 23-26, 2003.
7. Yiyun C, Zhenhua X, Minglu M and Tonguen X, "Dendrimers as Drug Carriers: Applications in Different Routes of Drug", J.Pharma.Sci.,97(1), 123-143, 2008.
8. Hawker C and Fréchet J.M.J, "A new convergent approach to monodisperse dendritic molecule" J. Chem. Soc. Chem. Commun., 15, 1010-1012, 1990.
9. Hawker C, Wooley K.L and Fréchet J.M.J, J.Chem. Soc. Perkin. Trans.,1, 1287-1289, 1993.
10. Frechet J.M.J and Tomalia D.A, "Introduction to the Dendritic state", Dendrimers and other Dendritic Polymers, John Wiley & Sons Ltd,24-23, 2001.
11. Sonke S and Tomalia D.A, "Dendrimers in biomedical applications reflections on the Field" Advanced Drug Delivery Reviews, 57, 2106-2129, 2005.
12. Barbara K. and Maria B., "*Review* Dendrimers: properties and applications", Acta Biochimica Polonica, 48 (1), 199–208, 2001.
13. R.P.Patel et al. "Dendrimers: A new innovation in drug delivery", Pharma Bio World, 42-52, 2007.
14. Gillies E.R. and Fréchet J.M.J, "Dendrimers and dendritic polymers in drug delivery" Drug Discovery Today, 10, 35-43, 2005.
15. Mohammad N and Antony D, "Crossing cellular barriers using dendrimer nanotechnologies", Current Opinion in Pharmacology, 6, 522–527, 2006.
16. LeeS.C "Dendrimers in Nanobiological Devices" Dendrimers and other Dendritic Polymers Edited by Fre´chet J.M.J and Tomalia D.A., 547-554.