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Review Article

Synthesis, Properties and Application as a Possible Drug Delivery Systems Dendrimers – A Review

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A B S T R A C T

Dendrimer is derived from the Greek word "dendron" which is used for tree and from the Greek suffix "mer" (segment) which describes the synthetic, three-dimensional molecules having branching parts."A dendrimer is generally described as a macromolecule, which is characterized by its dendritic and hyper branched 3D structure that offers a high degree of surface functionality and versatility." Dendrimers possess three distinguishable architectural components i.e. an interior core, interior layer(generations) composed of repeating units radially attached to the interior core, and exterior (terminal functionality) attached to outermost interior generation (Fig. 1). The higher generation dendrimers, due to their globular structure, occupy a smaller hydrodynamic volume compared to the corresponding linear polymers. The dendritic structure is characterized by layer between each generation.Dendrimers are generally prepared using either a divergent method or a convergent one. There is a fundamental difference between these two construction concepts. Dendrimers shows the various properties such as structure, shape, aqueous solubility, non-polar solubility, &architecture. Dendrimer can be classification on the basis of their shape, structure, branching, solubility, chirality and attachment. Dendrimer can be differentiated on the basis of their shape, end functional groups and internal cavities.

Key words: - Dendrimers, Properties, Classification, Types, And Application.

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INTRODUCTION: -

Dendrimer is derived from the Greek word "dendron" which is used for tree and from the Greek suffix "mer" (segment) which describes the synthetic, three-dimensional molecules having branchingparts.[1]"A dendrimer is generally described as a macromolecule, which is characterized by its dendritic and hyper branched 3D structure that offers a high degree of surface functionality and versatility."[2]Dendrimers possess three distinguishable architectural components i.e. an interior core, interior layer (generations) composed of repeating units radially attached to the interior core, and exterior (terminal functionality) attached to outermost interior generation (Fig. 1). The higher generation dendrimers, due to their globular structure, occupy a smaller hydrodynamic volume compared to the corresponding linear polymers. The dendritic structure is characterized by layer between each generation.[3]

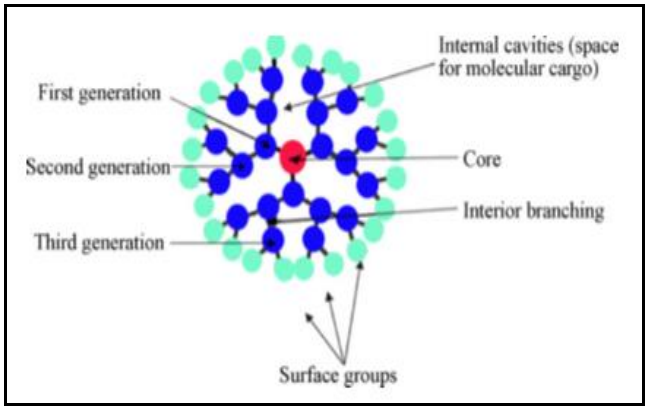

Figure 1: General structure of dendrimers.

HISTORY OF DENDRIMERS: -

The first dendrimers be completed by divergent synthesis advanced by Fritz Vogtle in 1978, R.G. Denkewalter at

AlliedCorporation in 1981, Donald 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. A lot of research has already been completed by studying the different properties and application of dendrimers but a lot of researchers still believe it to be in its initial stages. [4]

SYNTHESIS: -

Dendrimers are generally prepared using either a divergent method or a convergent one.[5] There is a fundamental difference between these two construction concepts.

DIVERGENT METHOD: -

In the divergent methods, dendrimer grows outwards from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first-generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built layer after layer (Fig. 2A). Thedivergent approach is successful for the production of large quantities of dendrimers. Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. It causes some difficulties in the purification of the final product.

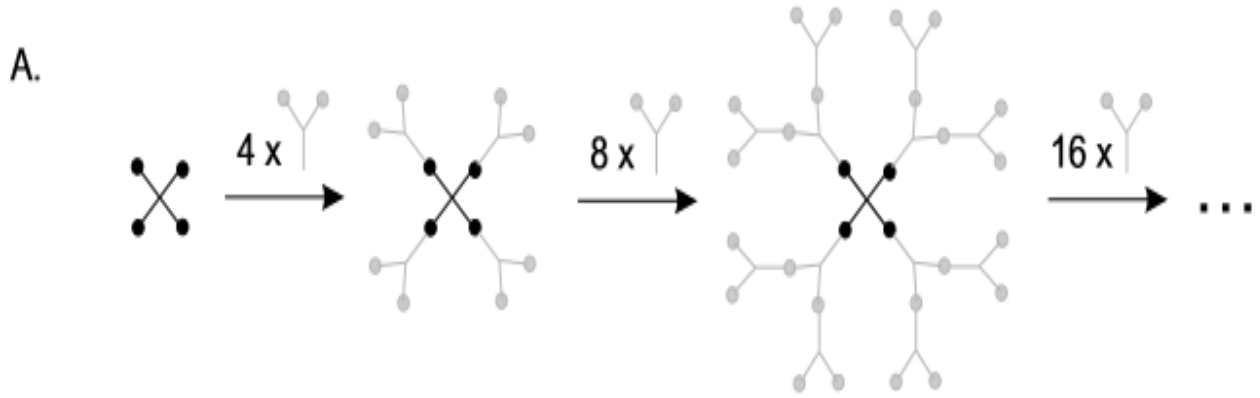

Figure: 2A.The divergent growth method.

CONVERGENT METHODS: -

The convergent methods were developed as a response to the weaknesses of the divergent synthesis.[6] In the convergent approach, the dendrimer is constructed stepwise, starting from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule (Fig. 2B). The convergent growth method has several advantages. It is relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised. It becomes possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecule. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule.

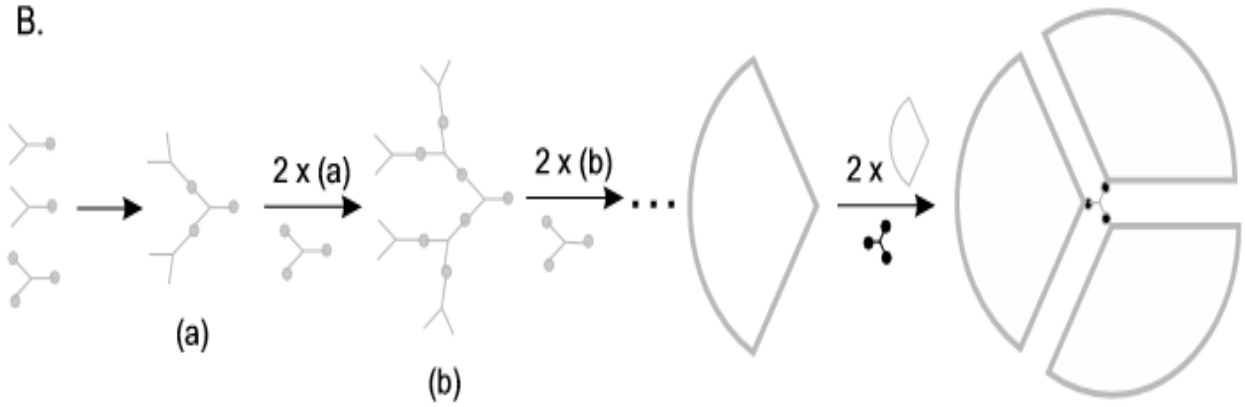

Figure: 2B. The convergent growth method

PROPERTIES OF DENDRIMER: -

Some of the most important properties of dendrimers and linear polymer like structure, shape, structural control, architecture etc shown in the table no. 1

Table: 1 Properties of Dendrimer and linear compact.[7]

Sn no.	Property	Dendrimer	Linear polymer
1.	Structure	Compact, Globular	Not compact
2.	Synthesis	Careful & stepwise growth	Single step polycondensation
3.	Structural control	Very high	Low
4.	Architecture	Regular	Irregular
5.	Shape	Spherical	Random coil
6.	Crystallinity	Non–crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7.	Aqueous solubility	High	Low
8.	Non-polar solubility	High	Low
9.	Viscosity	Non-linear relationship with molecular weight	Linear relation with molecular weight
10.	Polydispersity	Monodisperse	Polydisperse

CLASSIFICATION OF DENDRIMER: -

Dendrimer can be classification on the basis of their shape, structure, branching, solubility, chirality and attachment, which can be classified in table no. 2.

Table: 2 Classification of dendrimers. [8]

S. No.	Classification of dendrimers	Application/Method
1	Simple Dendrimer	They have simple monomer units. The convergent synthesis of a sequence of monodisperse are lester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 and 46 benzene rings linked symmetrically and have molecular diameters of 45 A.
2	Liquidcrystalline dendrimer	These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer. Functionalization to the end group of carbosilane dendrimers with 36 mesogenic units which can be attached through a C-5 spacer, and leads to liquid crystalline dendrimers that form broad smectic phase in the temperature range of 17°C to 130°C.
3	Chiral dendrimer	In chiral dendrimers the chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core e.g. chiral dendrimers obtained from pentaerythritol.
4	Micellar dendrimer	These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a collection of aromatic polymeric chain which able to generate an environment that resembles some micellar structures, which forms complex with small organic molecules in water.
5	Hybrid dendrimer	These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. Which provide an opening to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers.
6	Amphiphilic dendrimer	These are the class of globular dendrimers that have asymmetrical but highly controlled division of chain end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion.
7	Metallo dendrimer	Dendrimers attached with the metal ion to form the complexation either in the interior or on the peripheral, which may be regarded as metallodendrimers. The ruthenium bipyridine complex based dendrimer have attribute electrochemical and luminescence properties.

TYPES of DENDRIMERS: -

Dendrimer can be differentiated on the basis of their shape, end functional groups and internal cavities, which can be classified in table 3.

Table: 3 Types of Dendrimers

S No.	Types of Dendrimer	Synthesis	Examples	Identification
1	PAMAM (Poly Arnido Amine) Dendrimer	Divergent	Dendritech™ (USA)	These are spheroidal or ellipsoidal in shape. (9) It has high solubility and reactivity due to incidence of a number of functional end groups and empty internal cavities. [10-11]
2	PPI (Poly Propylene Imine) Dendrimer	Divergent	Asramol by DSM (Netherlands)	Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as center. These are commercially available up to G-5 and are extensively used in material science and biology. [12]
3	Chiral Dendrimer	Convergent	chiral dendrimers derived fromPentaerythritol	The chirality of the dendrimers was based upon the building of constitutionally different but chemically alike branches to chiral core. [13]
4	Multilingual Dendrimers	Convergent	VivaGel	These are the dendrimers which hold multiple copies of a particular functional group on their surface. [14]
5	Tecto Dendrimers	Divergent	Stratus® CS Acute Care™, Starburst®, Mercapto	These were made up of core dendrimers, which can be surrounded by other dendrimers, which execute a specific function leading to a smart therapeutic system used for diagnose the diseased state and deliver API to the accepted diseased cell.
6	Hybrid Dendrimers	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes	These dendrimers have characteristic of both dendritic and linear polymer.
7	Amphiphilic Dendrimers	Divergent	SuperFetch,Hydra amphiphiles andbola-amphiphiles	These have one half that is electron donating and another half is electron retreating.
8	Peptide Dendrimers	Convergent	Beta Casomorphin (human)	Peptide dendrimers are those which hold amino acid as branching or interior unit. These are used for the diagnostic purpose and vaccine delivery. [15]
9	Frechet-Type Dendrimers	Convergent	Frechettype dendronazides, ™Priostar	These were based on polybenzyl etherhyper branched skeleton. Carboxylic acid group attached on the surface of dendrimers that provides site for further functionalization and also improve the solubility of dendrimers.
10	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergent	SARSOX	These are silicon containing commercial dendrimers which are inverted unimolecular micelles and contains exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamine.
11	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	vaccine and diagnostic research	These are dendron-like molecular assembly based upon apolylysine frame. Lysine with its alkyl amino side-chain performed as a excellent monomer for the overture of frequent branching points.[16]

APPLICATION OF DENDRIMERS: -

Dendrimers have some of the following applications. Such as-

Dendrimers in biomedical field: -

The dendritic polymer has advantage in biomedical applications. These dendritic polymers are analogous to protein, enzymes and viruses and easily functionalized. Dendrimers and other molecules can either be attached to periphery or can be encapsulated in their interior voids. The dendrimer should possess certain qualities for its utility as biological agents. The dendrimer should be nontoxic, non-immunogenic, bio permeable, able to target specific structure. Due to specific synthesis, Polyamidoamine (PAMAM) dendrimers possess the interesting properties, which distinguish it from classical linear polymers and are the most studied starburst macromolecule. PAMAM dendrimers can also be used to target tumour cells. Targeting groups can be conjugated to the host dendrimers surface [17] to allow the imaging agent to bond selectively to specific site such as receptors on tumour cell to improve detection. Cisplatin was complexed to the surface groups of a carboxylate-terminated PAMAM dendrimer which led to a tenfold increase in the solubility of cisplatin compared to the free drug [21]. It was also found that the use of lower molecular weight dendrimers with denser interiors and ellipsoidal, flattered or elongated shaped may result in improved dendritic MRI contrast agents.

Dendrimer as magnetic resonance imaging contrast agents: -

Dendrimer based metal chelates act as a magnetic resonance imaging contrast agent. Dendrimers are highly

suited and used as image contrast media because of their properties. Many tests carried on dendrimershave shown that dendrimers are stronger contrast agent than conventional ones. They can improve visualisation of vascular structure in magnetic resonance angiography (MRA) of the body. Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged enhancement with a half-life of 200 min compared to 24 min for monovalent gadolinium agent. This prolonged enhancement time is extremely useful for3D time-of-flight MR angiography [18]. In the recent study, it was found that the molecular size of a dendrimer-based MRI agent altered the route of excretion. Contrast agents having molecular weight less than 60 kDa were excreted through kidney being potentially suitable as functional renal contrast agents. Larger sized and hydrophilic contrast agents were found better for use as blood pool contrast agent. Larger hydrophilic agents were useful for lymphatic imaging. Finally, these dendrimer-based MRI agents were recognised by the pharmaceutical industry which results in various commercial developments.

Dendrimers in Antitumor Therapy: -

Dendrimers molecule has found use as diagnostic reagent for tumour imaging by magnetic resonance imaging and as contrast agent; by varying the size and hydrophilicity and by combining with tumour targeting antibodies, these compounds can be used for a range of specific imaging purpose. [19] The drug used should be non-toxic, under nonirradiative condition, thus acting as prodrug when not irradiated. Dendrimers containing photosensitises named 5- aminolaevulinic acid has been attached to the surface of dendrimers and studied as an agent for photodynamic therapy (PDT) of tumorigenic keratinocytes. [20] The administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue were involved in cancer treatment. Also, glycodendrimer constitute an important class of therapeutic molecules. The dendrimers were investigated with the purpose of producing a drug that would interact with carcinoma derived Tantigen-binding receptors to interfere with carcinoma growth. This type of Glycodendrimer reacted in a generation dependent way with monoclonal antibodies against the T-antigen with higher generation

having higher affinities. The therapeutic uses of dendrimers may be within the cancer field where numerous examples of targeting tumours for diagnostic purpose have been described and where it is possible to define a cancer specific cell surface component that can be targeted.

Dendrimers in transdermal drug delivery: -

Transdermal drug delivery has come into existence long back. To improve the effectiveness of the drug transdermal drug delivery system was emerged. Drug delivery through skin to achieve a systematic effect of drug is known as transdermal drug delivery. Transdermal delivery provides controlled, constant administration of the drug which extends the activity of drug having short half-life through the reservoir of drug present in the delivery system and its controlled release characteristics.[22] The drug which is to be delivered should have low melting point, should be potent, having short half-life and non- irritating. PAMAM dendrimer complex with Non-Steroidal Anti-inflammatory Drugs (e.g. Ketoprofen, Diflunisal) which are very effective in treatment of acute and chronic rheumatoid and osteoarthritis, could be improving the drug permeation through the skin as penetration enhancers.[23] The model drugs Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies.

Dendrimers in ocular drug delivery: -

The topical application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. An ideal ocular drugdelivery system should be non-irritating, biocompatible, sterile, isotonic and biodegradable. [24] The recent problems for ocular drug delivery focus on increasing the residence time of pilocarpine in the eye was overcome by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface modified dendrimers were predicted to enhance pilocarpine bioavailability. [25-26]

Dendrimers in targeted drug delivery: -

Targeted drug delivery is a method of introducing medicine to a patient in a way that increases the attentiveness of medication in meticulous part of body. Dendrimers have multifunctionality and high possibilities for drug delivery applications as they have high density and wide range of functional groups on its surface. Due to the twice functional group, the plasma level of the drugs will persist at desired level for longer phase of time and increase its pharmaceutical effectiveness. Generally, the therapeutic effectiveness of drug is diminished due to low bioavailability, insolubility, toxicity and the decomposition of drug under biological circumstances [28]. Using Dendrimers, targeting moieties against conjugated drug molecule, the above shortcomings can be overcome.

Dendrimers in oral drug delivery: -

Oral drug delivery is the most favourable and has arriving more attention in the pharmaceutical field because of broadmindedness of production, low cost, expediency of easiness of administration and suppleness in formulation of dosage form. The controlled release method for the oral use are mainly solids and based on dissolution, diffusion or a mixture of both mechanisms in the control of release rate of drug [29]. One significant advantage of oral drug delivery is less fluctuating plasma drug level is maintained with controlled drug delivery systems, because the drug is gradually released from the dosage continuously and maintains the stable blood level. Along with the advantages there are some disadvantages of oral delivery route i.e. low solubility in aqueous solutions and low diffusion across intestinal membranes [30]. Emanuele and his researcher investigated that the result of dendrimer generation and conjugation on the cytotoxicity, penetration and transfer mechanism of PAMAM dendrimer [31]. As the concentration and generation increased, the increase in cytotoxicity and penetration of dendrimers resulted. While reducing in cytotoxicity was experienced by conjugation with lauryl chloride.

Dendrimers for additives, printing inks and paints: -

Dendrimers can be used in toners material with additives, which required less material than their liquid counterparts. Xerox Corp. Patented a dry toner compound dendrimer as charge increasing species in the form of preservative [32].

Using preservative in printing inks, dendritic polymers certify to uniform linkage of ink to polar and non-polar foils. Use of Dendrimer additives in the composition of the innovation is efficient for varying the surface characterization of thermo plastic resin after moulding. One of example for this is polycarbonates, which are extensively used as an engineering thermoplastic for providing an exclusive grouping of toughness, rigidity, high softening temperature and processability.

Dendrimers in light harvesting material: -

An important research has been of great attention for designing molecules with controlled movement of charges. Most of the literature account shows direction towards energy funnelling from the chromospheres in the periphery to other chromospheres at the core [32]. A study on π conjugated dendrimers family based on truxene and thienyl ethynylene were manufactured.

Dendrimers as Catalyst: -

Dendritic polymers have been used in large amount as catalyst. There are two most important reasons for the benefit of using dendritic polymers. One of the reasons is opportunity of creating a large dendrimer with many active sites. These types of catalyst are an in-between heterogeneous and homogeneous catalyst which can be removed easily by filtration [33]. The second important reason is that, there is option of encapsulating a single catalytic site whose performance can be improved by dendritic superstructure [34]. Cooper and co-workers [35], synthesize fluorinated dendrimers which are soluble in supercritical CO2 that can be used to extract powerfully hydrophilic compounds from water into liquid CO2.

Dendrimers as an Optical Sensing: -

The necessity for improving sensor proceeding is always approaching towards explores new materials. Subsequent the birth of dendrimers, the opportunity was recognized by means of improving optical sensor technology. More important aspects are their twomost important structural properties i.e. 3D structure and numerous terminal functional groups. Introduction to dendrimers is provided with the focus on PAMAM dendrimers and optical sensors. Current trends have been analysed in those PAMAM dendrimer-based optical sensors used for pH, cations, and another analyte detection [4].

Dendrimer applications in various fields: -

Countless applications involving dendrimers are being researched worldwide. The following is an extensive list of the most common dendrimer applications. [2]

I. Power/Energy: -

Catalytic agent.[2]

II. Healthcare/Medical: -

- Cellular Transport
- Artificial cells
- Diagnostics and analysis
- Targeted delivery (e.g. protein, antibody and anti-inflammatory; nanoparticles,
- Radionucleides, fluorescent markers, etc.)
- MRI contrast agents (e.g. organ, vascular and tumor imaging)
- Transfection reagents, DNA-carriers
- Protein / enzyme mimics or modelling
- Manufacture of artificial bones
- Development of topical microbicide creams; antimicrobial, antiviral (e.g. for use against HIV) and antiparasitic agents
- Biomedical coatings (e.g. for artificial joints)
- Novel polyvalent dendrimer-based drugs
- Artificial antibodies and biomolecular binding agents, e.g. anti-infection and toxin treatment for SARS / bird flu (especially blocking the cytochine storm),
- Biowarfare, antibiotic-resistant drugs, etc. (2)

III. **Engineering: -**

- Molecular weight and size standards
- Chemical / biological sensors & detectors
- Carbon fiber coatings and ultra-thin film
- Polymer and plastics additives (e.g. for lowering viscosity, increasing stiffness, incorporating dyes, compatibilizers, etc.) Creation of foams (i.e. synthetic zeolites or insulating material)
- Building blocks for nanostructured materials.

IV. **Consumer Goods: -**

- Ink / laser-printing toners
- Dyes and paints
- Industrial adhesives
- Manufacture of nanoscale batteries and lubricants. [2]

V. Environmental: -

- Decontamination agents (trapping metal ions)
- Ultrafiltration. [2]

VI. **Electronics / Optoelectronics: -**

- Molecular electronics for data storage
- 3-D optical materials
- Light-harvesting systems
- OLEDs (i.e. flat panel displays and other light emission applications)
- Quantum dots
- Liquid crystals
- Printed wire boards
- Low-k materials (i.e. insulation materials). [2]

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