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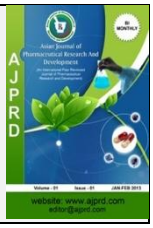

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Review Article

Dendrimers: Potential Drug Carrier For Novel Drug Delivery System

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ABSTRACT

Dendrimers are new effectiveness of polymeric substances. They are relatively branched, monodisperse macromolecules. Structural Advantages permit dendrimers to play a critical function inside the fields of nanotechnology, pharmaceutical, and medicinal chemistry. As a result in their precise behavior dendrimers are suitable for a wide variety of biomedical and commercial packages. The paper gives a quick evaluation of dendrimers' physicochemical properties and their possible use in various regions of research, generation, and treatment.

Keywords: Dendrimer, PAMAM (Poly Amido Amine) Dendrimer, PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers, PPI (Poly Propylene Imine) Dendrimer

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INTRODUCTION

Dendrimers are a singular class of structurally controlled macromolecules that have the shape like a tree or star form, with a critical center, interioroutlets, and terminal groups enhance the surface and from the hollow space inside the middle. Dendrimers have properly defined length, shape, molecular weight, and monodispersity, and reactivity is decided through shells and chemical composition of the core, within branching, and surface functionalities. It haspronged mono-dispersed polymer having 5-50 nanometers in diameter with distinctive structural and topological features, via these residences, now a day it has great attention from both scientists and researchers. Dendrimers are just in between molecular chemistry and polymer sciences.[1-4] Dendrimer oligonucleotide isa specialist of a new section of polymer science, frequently been referred to as the —Polymers of the 21 century. Dendrimer chemistry turned into first added in 1978 by way of Fritz Vogtle and coworkers. He synthesized the primary cascade molecules‖ later it becomes known as a dendrimer. The phrase —dendrimer originated from two words, the Greek word dendron, which means tree, and meros, that means component. Newkome's and coworkers independently stated the synthesis of comparable macromolecules. They referred to as thearborols from the Latin phrase arbor'alsomeaning a tree.[5, 6]Dendritic polymers are nanostructures, which might be suitable for drug solubilization applications, transport of DNA and oligonucleotide, targeting drug at particular receptor website, and capacity to behave as a facility for the development of drug delivery device. Dendrimers are core-shell nanostructures with a particular structure and low polydispersity, which are synthesized in a layer-with the aid of-layer approach (expressed in ‗generations') around a core unit, ensuing in the high level of manipulating oversize, branching points and surfaceability. The potential to adapt dendrimer properties to therapeutic needs makes them the best carriers for small molecule drugs and biomolecules. Dendrimers are being considered as components in numerous routes of administration, which include intravenous, oral, transdermal, pulmonary, and ocular.[7-11]

STRUCTURE OF DENDRIMER

Dendrimers are fabricated from a beginning atom, inclusive of nitrogen, to which carbon and other elements are delivered by using a repeating sequence of chemical reactions for the production of a circular branching structure. As the procedure repeats, successive layers are brought, and the field can be improved to the dimensions required with

the aid of the investigator. The result is a spherical macromolecular shape whose length is just like albumin and hemoglobin, however smaller than such multimers because of the huge IgM antibody complex. The performance of these dendrimers is established upon its length, generation, and surface useful corporations with successful in dendrimer generation the dendrimer, the dendrimer development linearly while the quantity of surface group will increase exponentially.[12-14]

Typical dendrimers are globular nanoscale macromolecule with a selected structure produced from three distinct regions as proven in (Figure 1).

- An initiator center.
- Interior layers (generations) composed of repeating implements, considerably attached to the interior core.
- Exterior (terminal capability) is attached to the outermost interior generations.

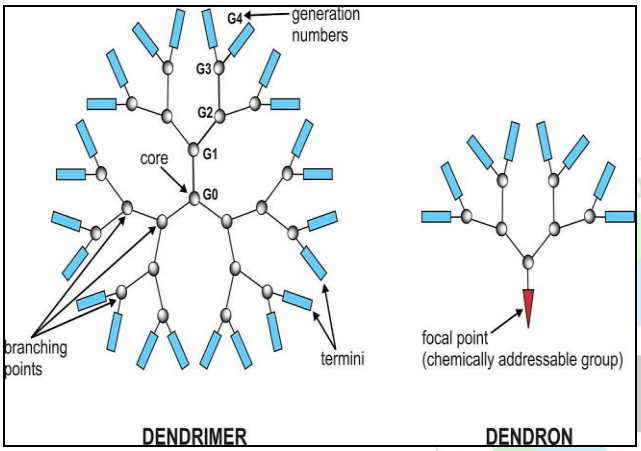

Figure 1: Structure of dendrimers [12]

ADVANTAGES OF DENDRIMERS

- Dendrimers give diverse benefits over other polymers:
- Dendrimers have nanoscopic particle length ranges from 1 - 100 nm, which makes them less susceptible to reticulum endothelium uptake.
- They have a lower polydispersity index, due to stringent management in the course of synthesis. As the density of branches increases, the outermost branches set up themselves surrounding a lower density middle within the shape of spheres, the outer surface density is more, and most of the distance remains whole towards the center. This region can be applied for drug entrapment.
- Multiple functional groups are present on the outer surface of dendrimers, which can be used to attach vector devices for targeting to a particular site in the body.
- Dendrimers may be changed as stimuli attentive to release the drug.
- Dendrimers might show a better permeability and retention effect which lets in them to target tumor cells extra successfully than small molecules.
- They may be synthesized and designed for unique packages. Due to their feasible topology, capability and dimensions, they are perfect drug transport systems; and also, their length is very close to diverse important biological polymers and assemblies along with DNA and proteins which are physiologically perfect.[15-17]

SYNTHESIS OF DENDRIMERS

Dendrimers are typically organized using both a divergent or a convergent technique. There is an essential difference between those two creation methods. [3, 11, 18-20]

Divergent method

In this approach, dendrimer develops from a multifunctional middle molecule. The response of the core molecule with monomer molecules, which incorporates one reactive and dormant group, shaped the first generation dendrimer. Then this new outer edge of the first-generation dendrimer is activated for reactions with extra monomers. The methodis repeated for several generations and a dendrimer is constructed after numerous layers of response. The divergent technique is of greater use for the production of massive quantities of dendrimers. Issues occur from side reactions and incomplete reactions of the end groups that lead to structural defects. To avoid side reactions and to force reactions to completion large excess of reagents is required. It causes some complications in the refining of the final product (Figure 2).

Convergent method

The convergent techniques have been advanced as to decrease the issues of the divergent synthesis. In the convergent technique, the dendrimer is built stepwise, beginning from the end groups and progressing inwards. When the dendrons are developed, they may be connected to a multifunctional middle molecule (Figure 2). The convergent growth approach has several benefits. It is extra suitable to purify the desired product and the incidence of defects inside the final structure is minimized. By this method formation of refined engineering into the dendritic shape through specific placement of purposeful businesses on the periphery of the macromolecule is feasible. This approach does now not permit the formation of high generations due to the fact steric issues occur within the reactions of the dendrons and the middle molecule.

Double exponential and mixed growth

The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the idea and implications of 'double exponential' growth. Double exponential growth, similar to a speedy increase method for linear polymers, involves an AB2 monomer with orthogonal protecting groups for the A and B functionalities. This approach permits the preparation of monomers for each convergent and divergent increase from a single start material.

These products are reacted together to offer an orthogonally protected trimer, which can be used to copy the increase method once more. The energy of double exponential growth is greater diffused than the potential to build massive dendrimers in noticeably few steps. In reality, double exponential growth is so rapid that it can be repeated simplest or possibly three instances earlier than further increase will become impossible. The double exponential technique offers a way wherein a dendritic fragment may be extended in both the convergent and the divergent path as required. In this way, the perfect basics of each procedure

may be accessed without the need to bow to their shortcomings (Figure 2).

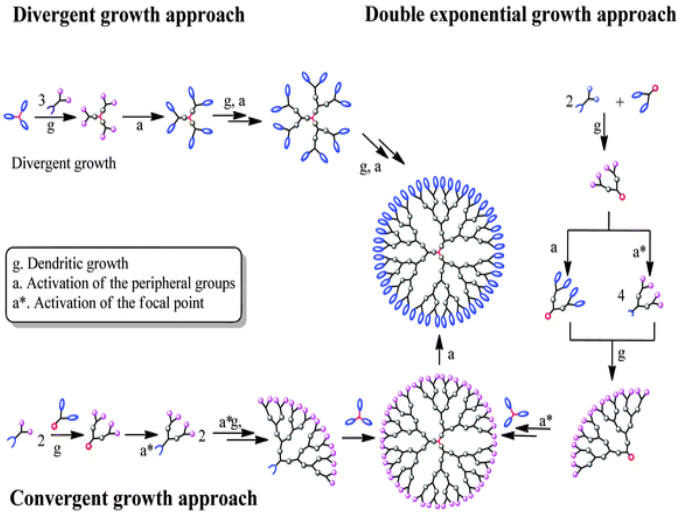

Figure 2: Synthetic methods for building dendritic macromolecules (Dendron's): divergent growth approach, convergent growth approach, double exponential growth approach.[3, 2111]

Hypercores and branched monomers boom

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields.

PROPERTIES OF DENDRIMERS

1. Nanoscale sizes which have similar dimensions to vital bio-building blocks as an example, proteins, DNA.
2. Numbers of terminal surface groups appropriate for bio-conjugation of drugs, signaling corporations, concentrated on moieties or biocompatibility businesses.
3. Surfaces that can be designed with determined administrations to reinforce or face up to trans-mobile, epithelial or vascular bio-permeability.
4. An interior void space may be used to encapsulate small-molecule pills, metals, or imaging moieties. Encapsulating in that void space reduces the drug toxicity and helps managed release.
5. Positive biocompatibility patterns, which are associated with lower phase anionic or neutral polar terminal surface groups, compared to higher generation impartial polar and cationic surface groups
6. Non- or low-immunogenicity associated with most dendrimer surfaces changed with small functional groups or polyethylene glycol (PEG).
7. Surface groups that may be changed to optimize bio-distribution; receptor-mediated focused on, therapy dosage or controlled release of drug from the in the interior space. [22-24]

FACTORS AFFECTING DENDRIMER PROPERTIES

Effect of pH

The take a look at of structural behavior of PAMAM dendrimers as a feature of pH, by applying molecular dynamics display that the dendrimer has a prolonged conformation, based on a noticeably ordered shape at low pH (pH<4). At this pH, the interior is getting progressively "hollow" as the generation number increases as a result of repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior. 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. At higher pH (pH>10) the dendrimer agreement as the price of the molecule will become impartial, acquiring a more round (globular) structure, in which the repulsive forces among the dendrimer hands and the floor groups reaches aminimum. At this pH, the conformation has a better degree of back-folding on account of the susceptible "inter-dendron" repulsive forces.[25-27]

Effect of solvent

The solvation power of any solvent to solvate the dendrimer is a completely essential parameter while investigating the conformational state of a dendrimer. Dendrimers of all generations commonly showcase a larger quantity of returned-folding with reducing solvent best, i.e. decreasing solvation. However, being more flexible, the low generation dendrimers show the very best tendency toward back-folding as a result of terrible solvation in comparison to the higher generation dendrimers. NMR studies carried out on PPI dendrimers concluded that a nonpolar solvent like benzene poorly solvates the dendrimers favoring intramolecular interactions between the dendrimer segments and back-folding. However, a weakly acidic solvent like chloroform can act as a hydrogen donor for the interior amines in a primary dendrimer like PPI, leading to an extended conformation of the dendrimer due to considerable hydrogen bonding between the solvent and the dendrimer amines. Both experimental, as well as theoretical studies on amino-terminated PPI and PAMAM dendrimers (polar dendrimers), display the tendency that nonpolar aprotic (poor) solvents result in better molecular densities in the middle location due to back-folding, whereas polar solvents solvate the dendrimer fingers and set off a higher molecular density on the dendrimer surface. Back-foldingof the polar surface groups can also reveal the extra hydrophobic dendrimer parts to the environment leading to a reduced surface polarity of the back-folded dendrimer.[27]

Effect of salt

High ionic strength (high concentration of salts) has a solid impact on charged PPI dendrimers and favors a becomeconcentrated conformation of dendrimers, with a high degree of back-foldingsomewhat similar to what is observed upon increasing pH or poor solvation. At low salt conditions, the repulsive forces among the charged dendrimer segments result in a prolonged confirmation which will decrease rate repulsion within the structure.[25]

Effect of concentration

In dendrimers with flexible structures,the conformation isn't always affectedby small molecules like solvents, salts, or protons, however, will also be sensitive to larger objects, including different dendrimers or surfaces that may have a great effect on at the molecular density and conformation of the dendrimer. Small-angle X-ray scattering (SAXS) experiments implemented on PPI dendrimers (G4, G5) in a

polar solvent like methanol show that the molecular conformation of dendrimers upon developing awareness turns into an increasing number of reduced in size. This molecular contraction might also limit the repulsive forces between the dendrimer molecules and increase the ability of the dendrimers to show a greater tight intermolecular packing.[28]

MECHANISM OF DRUG DELIVERY THROUGH DENDRIMERS

Due to the properly defined 3D structure and plenty of surface functional groups, drug molecules can be loaded both in the interior of the dendrimers in addition to attached to the surface groups as stated earlier. Dendrimers can feature as drug carriers both via encapsulating capsules within the dendritic shape or by interacting with drugs at their terminal functional groups thru electrostatic or covalent bonds forming prodrug.

There are extensively two mechanisms for drug transport:

1. The first one is via *in vivo* degradation of drug dendrimer covalent bonding which depends on the presence of suitable enzymes or an environment capable of splitting the bonds.
2. The second one is by using releasing the drug because of changes in the physical environment inclusive of pH, temperature. This technique is independent of the outside factors and takes location in cavities of the core (endo-receptor) or outer shell of the receptor (exo-receptor).[19, 29, 30]

CLASSIFICATION OF DENDRIMERS

Classification of dendrimer Application/Methods

Simple dendrimer: They have simple monomer units. The convergent synthesis of a sequence of monodisperse isLester dendrimer, primarily based upon symmetrically substituted benzene tricarboxylic acid ester is defined. These materials include 4, 10, 22 and 46 benzene rings connected symmetrically and have molecular diameters of 46 A.[31]

Liquid crystalline dendrimer: These are made from mesogenic monomers e.g.Mesogen functionalized carbosilane dendrimer. Functionalization to the end groups ofcarbosilane dendrimers with mesogenic devices thatmay be connected via a C-5 spacer, and ends in liquid crystalline dendrimers that form an extensive smectic phase within the temperature variety of 17°C to 130°C.[31]

Chiral dendrimer: In chiral dendrimers, the chirality is primarily based on the building of constitutionally assorted but chemically alike branches to an achiral middle e.g. Chiral dendrimers obtained from pentaerythritol.[31]

Micellar dendrimer: These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a group of an aromatic polymeric chain capable of generating an environment that resembles some micellar structures, which forma complex with small natural molecules in water.[31]

Hybrid dendrimers: These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. Which provides a gap to apply them as surface-active agents, compatibilizers, or adhesives, e.g. Hybrid dendritic linear polymers.[31]

Amphiphilicdendrimer: These are the magnificence of globular dendrimers that have the asymmetrical but exceptionally controlled division of chain-end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion.[31]

Metallodendrimer: Dendrimers connected with the steel ion to form the complexation either inside the interior or on the peripheral, which can be appeared as Metallodendrimers. The ruthenium bipyridine complicated based dendrimer has attribute electrochemical and luminescence residences.[31]

Table 1: Types of Dendrimers

S.No.	Types of dendrimer	Synthesis	Identification	Reference
1	PAMAM (Poly Amido Amine) Dendrimer	Divergent	Spheroidal or ellipsoidal. It has great solubility and reactivity due to the rate of several functional end groups and empty internal cavities. Example, Dendritech TM (USA)	14, 29, 32-36
2	PPI (Poly Propylene Imine) Dendrimer	Divergent	Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as the center. These are generally available up to G-5 and are widely used in material science and biology. Example, Asramol by DSM (Netherlands)	
3	Chiral Dendrimer	Convergent	The chirality of the dendrimers was based upon the structure of constitutionally different but chemically alike branches to the chiral core. For example, chiral dendrimers are derived from pentaerythritol.	
4	Multilingual Dendrimers	Convergent	These are the dendrimers, which hold numerous copies of a particular functional group on their surface. Example, VivaGel	
5	Tecto Dendrimers	Divergent	These were made up of core dendrimers, which can be surrounded by other dendrimers, which effect a specific function leading to a smart therapeutic system used to diagnose the diseased state and deliver API to the accepted diseased cell. Example, Stratus® CS Acute Care TM, Starburst®, Mercapto	
6	Hybrid Dendrimers	Divergent	These dendrimers have characteristics of both dendritic and linear polymer. Example, Hybrid dendritic linear polymer, Polysilsesquioxanes	
7	Amphiphilic Dendrimers	Divergent	These have one-half that is electron-donating and another half is electron retreating. Example, SuperFect, Hydraamphiphiles, and bola-amphiphiles	

8	Peptide Dendrimers	Convergent	Peptide dendrimers are those, which hold amino acid as branching or interior units. These are used for diagnostic purposes and vaccine delivery. Example, Beta Casomorphin (human)	
9	Frechet-Type Dendrimers	Convergent	Thesewere based on polybenzyl ether hyperbranched skeleton. The carboxylic acid group is attached to the surface of dendrimers that provides a site for further functionalization and also improve the solubility of dendrimers. Example, Frechet type dendronazides, TM Priostar	
10	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergent	These are silicon-containing commercial dendrimers which are inverted unimolecular micelles and contain exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamine. Example, SARSOX	
11	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	These are dendron-like molecular assembly based upon a polylysine frame. Lysine with its alkyl amino side-chain performed as an excellent monomer for the overture of frequent branching points. Example, vaccine and diagnosticResearch	

DENDRIMER DRUG INTERACTIONS

Different interplay mechanisms have been explored, and that they may be widely sub-divided into 3 types: easy encapsulations, electrostatic interactions, and covalent conjugations.

Simple encapsulation

The ellipsoidal or spheroidal form, empty inner cavities, and open nature of the structure of dendrimers make it viable to at once encapsulateguest molecules into the macromolecule interior. These empty internal cavities are hydrophobic, which makes it suitable to engage with poorly soluble capsules via hydrophobic interactions. Moreover, the nitrogen or oxygen atoms inside the internal cavities can have interaction with the drug molecules via hydrogen bond formation. Because of those unique properties, the relationship between the inner cavities of dendrimers and drug molecules may additionally contain these supramolecular interactions like bodily encapsulation, hydrophobic interaction, or hydrogen bonding.[37, 38]

Electrostatic interaction

The high density of functional groups like amine corporations and carboxyl groups on the surface of dendrimers have potential programs in enhancing the solubility of hydrophobic capsules through electrostatic interplay. The G3 PAMAM dendrimer with an ammonia coreis taken for instance. It has a much higher amino organization density when compared with classical linear polymers. Non-steroidal anti-inflammatory drugs with carboxyl organizations, together with ibuprofen, ketoprofen, diflunisal, naproxen, and indomethacin, had been broadly been complexed with dendrimers through electrostatic interactions. Some anticancer and antibacterial drugshave also been pronounced to be integrated by this class of interaction. The common assets of these drug molecules are that they're weakly acidic capsules with carboxyl agencies within the molecules.[39, 40]

Covalent conjugation

The presence of large numbers of functional groups at the surface of dendrimers makes them appropriate for the covalent conjugation of numerous drugs with applicable functional groups.

In this condition, the drug is covalently certain to dendrimers and its release occurs through chemical or enzymatic cleavage of hydrolytically labile bonds. The encapsulation of drug molecules inside hydrophobic voids or absorption of drugs to the surface of dendrimers via electrostatic interactions protects the chemical integrity and pharmacological properties of drug molecules, while covalent attachment of drugs to the surface groups of dendrimers over chemical bonds gives good control over drug release. This facilitates tissue targeting and manages drug delivery.[41]

CHARACTERIZATION OF DENDRITIC POLYMER

A.Spectroscopy and spectrometry strategies spectroscopy and spectrometry techniques of characterization of the dendritic polymer are as follows[42-47]

Ultra-violet-visible spectroscopy (UV-VIS): Provides records for monitoring the synthesis of dendrimers. The intensity of the absorption band is proportional to the variety of chromophoric devices.

Infrared spectroscopy (IR): Provides facts for habitual evaluation of the chemical modifications going on the surface of dendrimers.

Near infra purple spectroscopy: Provides records for the characterization of delocalize π-π stacking interaction between end organizations of changed PAMAM.

Fluorescence: Provides records for an increasing number of high Sensitivity of fluorescence used to quantify defects at some point in the synthesis of dendrimers.

Mass spectroscopy: Chemical ionization or fast atom bombardment used for the characterization of small dendrimers whose mass is underneath 3000 Da. Electrospray ionization is used for dendrimers that are capable of form solid multicharged species.

X-ray diffraction (XRD): Provides statistics to permit precise determination of the chemical composition, structure, length, and shape of Dendrimer.

B.scattering strategies scattering techniques for characterization of the dendritic polymer are as follows[48-51]

Small attitude x-ray scattering (SAXS): Provides facts approximately their average radius of gyration (Rg) in answer. The depth of the scattering additionally gives statistics at the association of polymer segments.

Small attitude neutron scattering (SANS): Provides get right of entry to the radius of gyration, but may also reveal greater correct facts than SAXS. The place of the finishing companies has additionally been decided via SANS experiments performed with PAMAM dendrimers and PPI dendrimers.

Laser mild scattering (LLS): It determines the hydrodynamic radius of dendrimers. Dynamic LLS is normally used for the detection of aggregates.

C.Microscopy methods for characterization of the dendritic polymer are[52-54]

Transmission microscopy: Electron or light produces images that intensify the original, with a resolution eventually limited by the wavelength of the source.

Scanning microscopy: It produces a picture through contact touch Q at some angstroms of a touchy canilever arm with a sample. Ex. Atomic force microscopy.

D. Size-specific chromatography: It permits the partition of molecules in step with length.[54]

E. Electrical strategies for characterization of the dendritic polymer are as follows[55-57]

Electron paramagnetic resonance (EPR): Quantitative determination of the substitution effectiveness at the floor of PANAM dendrimers.

Electrochemistry: It provides information about the opportunity of the interplay of electroactive endgroups.

Electrophoresis: It affords the statistics approximately the assessment of purity and homogeneity of several kinds of water-soluble dendrimers.

F.Rheology and physical properties rheology and physical residences used for characterization of the dendritic polymer are as follows[58-60]

Intrinsic viscosity: It is an analytical probe of the morphological shape of dendrimers.

Differential scanning calorimetry (DSC): It is used to detect the glass transition temperature relies upon on thy molecular weight, entanglement, and chain composition of polymers.

Dielectric spectroscopy (DS): Gives whole facts about molecular dynamic procedures (α-, β)

G.miscellaneous other techniques used of characterization of the dendritic polymer are as follows[61-64]

X-ray photoelectron spectroscopy (XPS): It gives specific facts approximately the chemical composition of dendrimers such as poly (aryl ether) dendrons or PAMAM dendrimers which became obtained the use of XPS. This method is most normally used for the characterization of layers.

Sedimentation technique: used for lactosylated PAMAM dendrimers, measurements of dipole moments for PMMH dendrimer.

Titrimetric: It is used for determining the number of NH2 quit businesses of PAMAM dendrimers.

PHARMACEUTICAL APPLICATIONS

Dendrimer in ocular drug delivery

PAMAM dendrimers with carboxylic or hydroxyl surface groups, enhancing residence time and enhance the bioavailability of pilocarpine in the eye. [24, 65]

Dendrimers in pulmonary drug delivery

Positively charged PAMAM dendrimers (G2 and G3 technology) elevated the relative bioavailability of pulmonary drug delivery of Enoxaparin.[66]

Dendrimer in transdermal drug delivery

Dendrimers are capable of enhancing drug properties including solubility and plasma circulation time via transdermal formulations and to deliver drugs successfully due to its distinctly water-soluble and biocompatible nature. For instance improving the drug permeation thru the skin though PAMAM dendrimer complicated with NSAIDs like Ketoprofen, Diflunisal, and stronger bioavailability of PAMAM dendrimers by using the use of indomethacin because of the model drug in transdermal drug application. [67, 68]

Dendrimer in oral drug delivery

Oral drug delivery studies the usage of the human colon adenocarcinoma cell line, that have indicated that low generation PAMAM dendrimers cross cell membrane through a combination of two processes, i.e. Paracellular transport and adsorptive endocytosis. Increase within the cytotoxicity and permeation of dendrimers when an increase in the concentration and generation. [69, 70]

Dendrimers in centered drug delivery

Dendrimers have ideal properties, which can be useful in the targeted drug-delivery system. For example, PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. [12]

Dendrimers for controlled launch drug delivery

Encapsulation of 5-fluorouracil into PAMAM dendrimers(G=4) changed with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate, and decreased hemolytic toxicity. Controlled release of the Flurbiprofenaffected by using the formation of a complex with amine-terminated technology 4 (G4) PAMAM Dendrimers. [71]

Dendrimers in gene delivery

Dendrimers are significantly used as a non-viral vector for gene delivery. Various polyatomic compounds together with PEI, polylysine, and cationic had been applied as non-viral gene providers. [72]

Dendrimer as a solubility enhancer

Dendrimers are unimolecular micellar nature, because of having hydrophilic exteriors and hydrophilic interiors and shape covalent as well as non-covalent complexes with drug molecules and hydrophobes and enhance its solubilization behavior. [73]

Cellular shipping the usage of a dendrimer carrier

PAMAM dendrimers with lauryl chains to decrease toxicity and enhance cellular uptake, for example, Dendrimer–ibuprofen complexes entered the cells rapidly compared with the pure drug, suggesting that dendrimers can correctly bring the complexes drug internal cells. [74]

Dendrimers as nano-drugs

Dendrimers as Nano-Drugs, useful as antiviral capsules against the herpes simplex virus can potentially prevent/reduce transmission of HIV and different sexually transmitted diseases (STDs) while Poly(lysine) dendrimers changed with sulfonated naphthyl groups. Show amazing antibacterial biocides against Gram-positive and Gram-negative bacteria when PPI dendrimers with tertiary alkylammonium groups are connected to the surface and Chitosan– dendrimer hybrids had been determined to be useful as antibacterial agents, carriers in drug delivery systems, and indifferent biomedical programs. [75]

Dendrimers as biomimetic artificial proteins

Dendrimers are often referred to as "artificial proteins" due to their dimensional length scaling, narrow size distribution, and other biomimetic properties. For examples, PAMAM family, they closely match the sizes and contours of many important proteins and bio assemblies like insulin (3 nm), cytochrome C (4 nm), and hemoglobin (5.5 nm) are approximately the same length and form as ammonia-middle PAMAM dendrimers generations 3, 4 and 5, respectively. Generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes and generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of organic cells. [76, 77]

Dendrimers as nano-scaffolds

Reducing the interaction with macromolecules from the body protection system, and imaging tags due to a high-quality platform provided for the attachment of cell-specific ligands, solubility modifiers, and stealth molecules via dendrimer surface. For example, folate– PAMAM dendrimers have been successfully used as carriers of boron isotopes in boron neutron-capture treatment of cancer tumors. [78, 79]

(B) Therapeutic utility

Dendrimers in photodynamic therapy (PDT)

Treatment of cancer consists of the administration of a light-triggered photosensitizing drug that selectively concentrates in diseased tissue. For example, the photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers. The photosensitizer 5-aminolevulinic acid was studied as an agent for PDT of tumorigenic keratinocytes. [11]

Dendrimers for boron neutron capture therapy (BNCT)

The radiation energy generated from the capture response of low-electricity thermal neutrons by using 10B atoms has been used effectively for the selective destruction of tissue. Due to their well-defined shape and multivalence, Dendrimers are a very absorbing compound for use as boron carriers. [11]

(C) Diagnostic application

Dendrimers as molecular probes

Due to their ideal morphology and specific characteristics, use as molecular probes. For Example, the immobilization of sensor units at the surface of dendrimers is a completely efficient way to generate an integrated molecular probe, due to their huge surface area and excessive density of surface functionalities. [80]

Dendrimers as X-ray comparison marketers

Dendrimers are currently beneath research as potential polymeric X-ray contrast agents. Potential dendritic X-ray contrast agents the usage of various organometallic complexes which include bismuth and tin are used to gain a high-resolution X-ray image, numerous diseases, or organs, including arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary and so on. [41, 81]

Dendrimers as MRI assessment sellers

Introduction of target particular moieties to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer evaluation agents, for example, folate conjugated Gd (III)–DTPA PAMAM dendrimer, which extended the longitudinal relaxation rate of tumor cells expressing the excessive affinity folate receptor. [82]

Dendritic catalysts / enzymes

Dendrimers are useful as nanoscale catalysts because of their mixture of high surface region and high solubility. Dendrimers have a multifunctional surface; all catalytic sites are continually exposed in the direction of the response aggregate, and by smooth ultra-filtration methods, may be recovered from the response mixture. Dendritic shells may be used to produce a microenvironment that is beneficial for catalysis or provide shielding for functional groups at the dendritic core. [83]

Industrial processes

Dendrimers can encapsulate insoluble substances, such as metals, and transport them into a solvent within their interior. For example, fluorinated dendrimers, which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from, water into liquid CO_2. This can also help develop Technologies wherein hazardous natural solvents are changed through liquid CO_2. [18]

Current and potential applications of dendrimers

- One dendrimer molecule has hundreds of possible sites to couple to an active species. This may allow researchers to attach each concentrated on molecules and drug molecules to equal dendrimer, which could

reduce the bad side impacts of medications on healthy cells.

- Modification of cell-cell interactions and gene expression (e.g.: alteration of transcription elements binding to DNA) New carrier machine for drug shipping (gels, selfassociating structures)
- Dendrimers normally involve conjugating other chemical species to the dendrimer surface which can function as detecting agents (such as a dye molecule), affinity ligands, concentrated on components, radioligands, imaging dealers, or pharmaceutically active compounds.
- Delivery of Nucleic acids, Encapsulated pills, and Covalently linked pills.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.
- Vaccines towards microorganisms, viruses, and parasites.
- Diagnostic reagents in serodiagnosis (systems with surface ligands), Biosensor systems (structures containing dyes, reactive molecules) magnetic resonance imaging (e.g.: gadolinium adducts). [83, 84]

DENDRIMER BASED PRODUCTS

Several dendrimer primarily based products have already been accepted by using the FDA and a few in Phase II scientific trials. Various dendrimer based products are: [85-87]

1. Alert ticket for Anthrax Detection
2. Priofect™, Priostar™, and Starburst for targeted diagnostic, therapeutic delivery for cancer cells
3. SuperFect for Gene Transfection
4. Stratus CS for Cardiac Marker
5. Vivagel for preventing HIV

FUTURE PROSPECTIVE

The key conclusion is that the high level of control over the design of dendrimer, their shape, branching length, and density, and their surface functionality, makes dendrimer perfect carriers for the different packages like drug delivery, therapeutic and diagnostic agent. Poor solubility, bioavailability, and permeability biocompatibility and toxicity may be overcomeby using it. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a massive kind of structure with reduced value in their manufacturing. Moreover, the excessive density of surface groupsallows attachment of focused on organizations as well as corporations that alter the answer behavior or toxicity of dendrimers. Research progresses, novel applications of dendrimers will develop and the future should witness an increasing number of commercialized dendrimer based drug delivery systems.

CONCLUSION

The high phase of control over the structure of dendrimers, their length, form, branching duration, and density, and their surface functionality, makes these compounds the best carriers in the biomedical application including drug transport, gene transfection, and imaging.Despite two decades since the discovery of dendrimers, the multi-step synthesis still needs great effort. Unless there is a significant breakthrough in this field, only a few applications for which the unique dendrimer structure is essential will pass the cost-benefit test. This review of the dendrimer, a complete drug carrier, clearly illustrates the potential of this new "fourth design class of polymers" and proves the high optimism for the future of dendrimers in this important field.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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