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Dendrimer Drug Delivery System

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ABSTRACT

Dendrimers are highly branched, nanoscale polymers that offer unique structural characteristics for drug delivery applications. Their multivalency, precise molecular architecture and adjustable surface functionalities facilitate enhanced solubility, stability and targeted delivery of therapeutic agents. This review provides an overview of dendrimer-based drug delivery systems, focusing on their structure, synthesis, mechanism of action and applications in medicine. This review discusses the advantages of dendrimers, such as their ability to encapsulate a wide range of therapeutic agents, control drug release, and enhance bioavailability. It also examines the potential for targeted drug delivery, which can minimize side effects and improve treatment efficacy, particularly in cancer therapy. This review also covers various methods of functionalizing dendrimers, including surface modification with targeting ligands and therapeutic agents.

KEYWORDS: Dendrimers Drug Delivery System, Structure of Dendrimer, Types of Dendrimers, Synthesis, Drug Encapsulation, Functionalization, Application

INTRODUCTION

Drug delivery is an important method of formulation that gives a choice of dosage form that enhances the bioavailability, enhances the solubility, targets the action and reduces the toxicity. One of the main approaches that fulfills the above criteria is Dendrimers.[1] The "dendrimer" is derived from the Greek words "Dendron," meaning "tree or branches," and "Meros," meaning “parts” referring to its tree-like branched structure.[2]

That consists of three major architectural components; core, generations and terminal group. The core is the central initiator molecule from which the dendrimer branches out. It can be a single atom or a small molecule with multiple reactive sites. Common core molecules include ammonia, ethylenediamine, and polyols. Dendrimers are constructed in a radial fashion through successive generations or layers of branching units. Each generation represents a new set of branched monomers attached to the reactive sites of the previous generation. The terminal groups define the surface properties and reactivity of the dendrimer and can be tailored for specific applications.[3]

In 1978, Sir Vogtle and his colleague's proposed dendrimers, marking the first successful synthesis of these structures. This was followed by Tomalia's independent development of divergent synthesis for macromolecules in 1984-1985, which resulted in the first complete PAMAM dendrimers. In 1990, Frechet introduced a convergent synthesis method.[4] Recently, there has been a growing interest in dendrimers in drug delivery systems. Dendrimers are polymers that feature an empty inner cavity, allowing for the encapsulation of hydrophobic drug molecules. The outer shell of dendrimers influences their reactivity, enabling modifications or conjugation with guest molecules. These unique characteristics make dendrimers particularly suitable for drug delivery. As highly branched, radially symmetric, nano-sized polymers, dendrimers are widely utilized in drug delivery applications. They are three-dimensional, monodisperse globular macromolecules with numerous functional groups on their surfaces. The high surface functionality of highly branched polymeric dendrimers improves the solubility, stability, density, and reduces the viscosity of various drugs. Dendrimers are applied in drug delivery systems, gene delivery, enhancing solubility and transdermal drug delivery as nanomaterials.[5]

STRUCTURE OF DENDRIMERS

Dendrimer formation begins with an atom, often nitrogen, to which carbon and other elements are added through a series of chemical reactions, resulting in a spherical, branched structure. The resulting dendrimers are similar in size to proteins like albumin and hemoglobin but smaller than larger complexes, such as the IgM antibody.

Dendrimers consist of three main components.

1. Initiator Multifunctional Core: The central component from which the dendrimer grows.

2. Interior Layers (Generations): Successive layers of branching units that extend radially from the core.

3. Exterior Surface Functional Groups: Terminal groups attached to the outermost layer, which can be modified to influence the dendrimer's properties and interactions.[6,7,8]

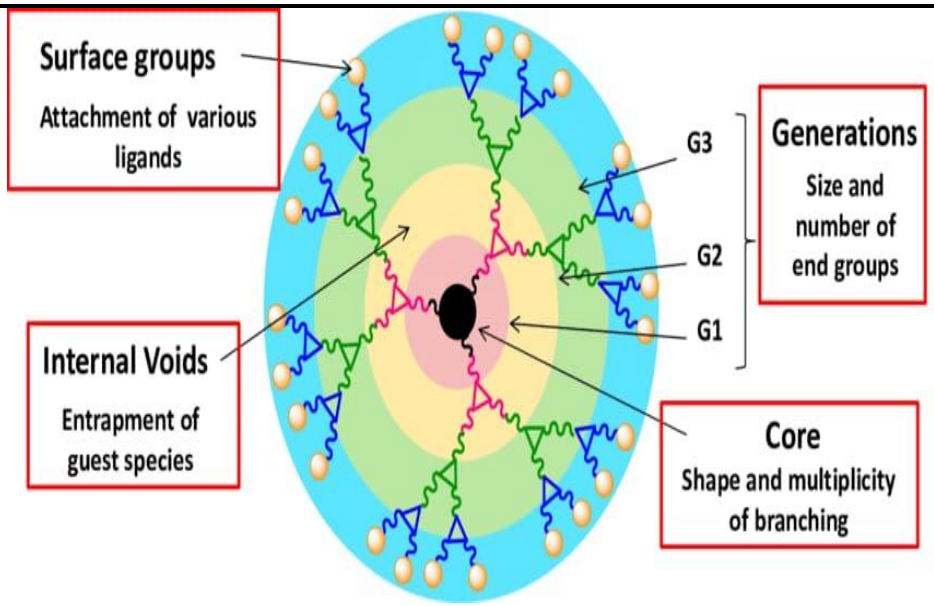

Figure 1: General Structure of Dendrimers

COMPONENTS OF DENDRIMERS

1. The Core

Interior layer (generations) made up of repeating units, radicals attach to the interior core.[9]

Exterior (terminal functionality) attaches to the outermost interior generations.[9]

2. The Pincer

Dendrimers feature various pincers on their outer shells, each created at the last branching point before reaching the surface. In Poly(propylene imine) (PPI) and Poly(amidoamine) (PAMAM) dendrimers, the number of pincers is halved compared to the total number of surface groups, as the chain splits into two at each branching point.[10]

3. Shell

Generation Space: The region between the branching points is known as the dendrimer shell or the homo-structural spatial segment.[11]

Shell Exterior: This outer shell extends from the final branching point to the surface.[11]

Internal Shell: The inner shell is contained within the dendrimer structure.[11]

4. The Generation

Homostructural layers form between the focal points (branching points) due to hyperbranching when moving from the center of the dendrimer to the periphery. Resulting in homostructural layers between branching points. The generation number indicates the number of focal points present in the dendrimer, counted from the core to the outer surface. For instance, a dendrimer with five focal points is designated as a 5^{th} generation dendrimer or G5-dendrimer. An example is the 5^{th} generation polypropylene amine, known as G5-PPI

dendrimer. The core of a dendrimer is often referred to as generation zero (G0), as it contains no focal points with hydrogen substituents not counted as such. Intermediates formed during dendrimer synthesis are sometimes called half-generations; for example, poly(amidoamine) (PAMAM) dendrimers that are terminated with carboxylic acid.[12]

5. End-Group

End groups is also known as terminal groups or surface groups, are the functional groups present at the outermost points of the dendrimer branches. These groups are crucial in determining the dendrimer's solubility, biocompatibility, and ability to interact with drugs. Dendrimers that have amine groups at the ends are referred to as amine-terminated dendrimers. These terminal groups can interact with drugs via various mechanisms, including electrostatic interactions, hydrogen bonding or covalent attachment. The specific functionalization of these end groups is vital in modulating the dendrimer's drug-delivery capabilities.[13]

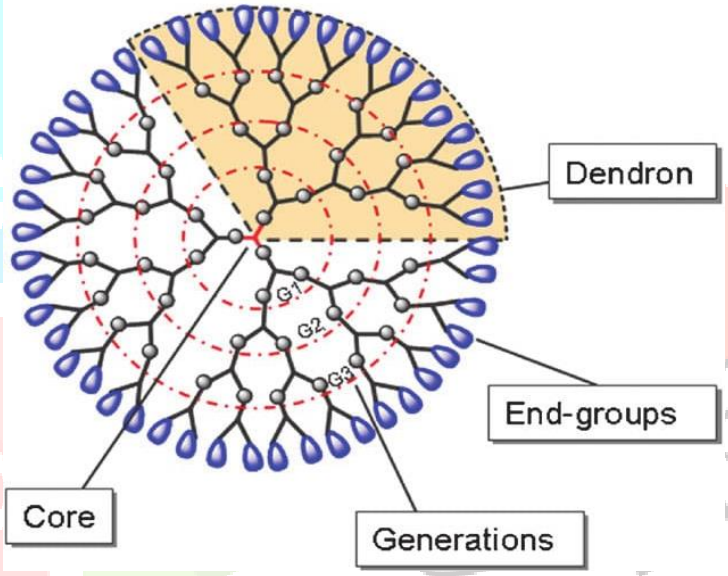

Figure 2: Components of Dendrimers

TYPES OF DENDRIMERS

Dendrimers can be classified based on their chemical structure, core composition, and the nature of branching units. Here are some common types of dendrimers.

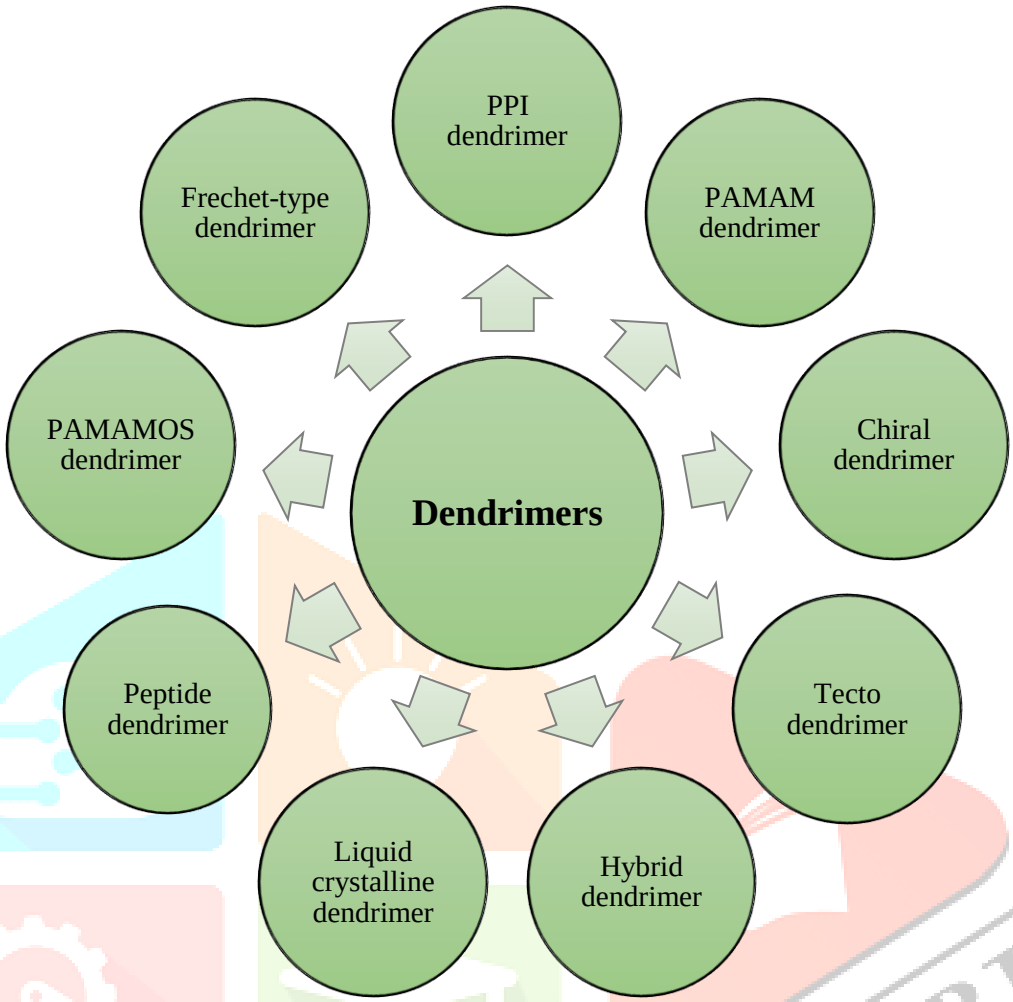

Figure 3: Types of Dendrimers

1. Poly(propylene imine) Dendrimers (PPI)

Poly(propylene imine) (PPI) dendrimers often incorporate poly-alkyl amines as terminal groups and contain multiple tertiary tris-propylene amines within their structure. They are commercially available up to generation G5 and find various applications in material science and biology, notably marketed under the name Astramol™.[14]

Ex: Asramol by DSM (Netherlands)

2. Poly(amidoamine) (PAMAM) Dendrimer

Poly(amidoamine) dendrimer i.e., PAMAM dendrimer are synthesis by divergent method by Fritz and Vogtle 1978. Starting from core initiators like ethylene diamine. These dendrimers exhibit a star-like, two-dimensional structure, particularly in high generations. They are commercially available in methanol solutions across generations G0-10, featuring five different core types and ten functional surface groups.[15]

Ex: Dendritech^{Tm} (USA)

3. Chiral Dendrimers

These dendrimers possess chirality due to the formation of branches that are intrinsically distinct yet nearly identical around a chiral center. They hold potential for use as chiral agents in enantiomer separations and as chiral catalysts for asymmetric synthesis.[16]

Ex: Chiral dendrimer derived from pentaerythritol

4. Tecto Dendrimer

Tecto dendrimer also called as core-shell dendrimer because tecto dendrimer are composed of a core dendrimer. Which may contain therapeutic agent or may not contain therapeutic agent and are surrounded by dendrimer each one of those perform a specific function leading to a smart therapeutic system.[17] Tecto dendrimer fix the target site and deliver API to the recognized diseases cell. Different component of tecto dendrimer perform different function ranging from diseased cell, recognition, diagnosis of diseases, drug delivery therapy.[5]

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

5. Hybrid Dendrimers

Hybrid dendrimers are composite structures formed by combining dendritic and linear polymers, either as block or graft polymers. These hybrids are created by fully monofunctionalizing the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, resulting in a unique polymer architecture with enhanced properties and functionality for various applications.[18]

Ex: Polysilsesquioxanes are a hybrid dendritic linear polymer.

6. Liquid Crystalline Dendrimers

These highly branched polymers possess a dendritic structure with mesogenic groups, enabling them to exhibit liquid crystalline behavior. They are made from mesogen-functionalized monomers, such as carbosilane dendrimers. This molecular design allows them to display distinct mesophase properties, demonstrating unique structural and functional characteristics in liquid crystalline phases.[19]

Ex: Mesogen-functionalized carbosilane dendrimers

7. Peptide Dendrimers

Multiple antigen peptide dendrimers represent a dendron-like molecular design utilized in various biological applications, including vaccine development and diagnostic research. These peptide dendrimers can also serve in drug delivery, act as contrast agents in magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), facilitate fluorogenic imaging and serological diagnostics.[20]

Ex: Beta Casomorphin (Human)

8. Poly(amidoamine-organosilicon) Dendrimers (PAMAMOS)

Discovered by Dr. Petar Dvornic in 1990, PAMAMOS dendrimers feature a unique structure that combines hydrophobic organosilicon (OS) shells with hydrophilic, nucleophilic poly(amidoamine) (PAMAM) interiors. Their symmetric network design allows them to complex and encapsulate various substances, presenting

significant potential for applications in nanolithography, photonics, chemical catalysis and electronics. They also serve as effective precursors for creating honeycomb-like networks with nanoscale Poly(amidoamine) (PAMAM) and organosilicon (OS) domains.[21]

Ex: SARSOX

9. Frechet-Type Dendrimers

Frechet-type dendrimer was synthesized by Hawker and Frechet. It consists of a poly-benzyl ether skeleton with a hyperbranched structure and carboxylic acid groups as terminal group.[22]

Ex: Frechet Type Dendron Azides, Priostar^{Tm}

METHODS OF SYNTHESIS

1. Divergent Method

2. Convergent Method

3. Double Exponential or Mixed Growth

4. Hypercores and Branched Monomer Growth

First two are the Main methods for synthesis of dendrimers. These methods play pivotal roles in tailoring dendrimer properties for various applications in drug delivery, nanotechnology and materials science. Both methods offer distinct advantages, allowing researchers to optimize dendrimer characteristics such as size, shape, surface functionality, and structural uniformity, making them highly important for a wide range of applications.

1. Divergent Method

The divergent method, introduced by Tomalia, involves synthesizing dendrimers from a core site. Initially, the core reacts with multiple moles of a reagent that has at least two branching sites. After removing the protecting groups, the first generation of dendrimers is formed. This process is iterated until the desired dendrimer size is achieved. The first dendrimers synthesized using this approach were PAMAMs, commonly referred to as starburst dendrimers.[23]

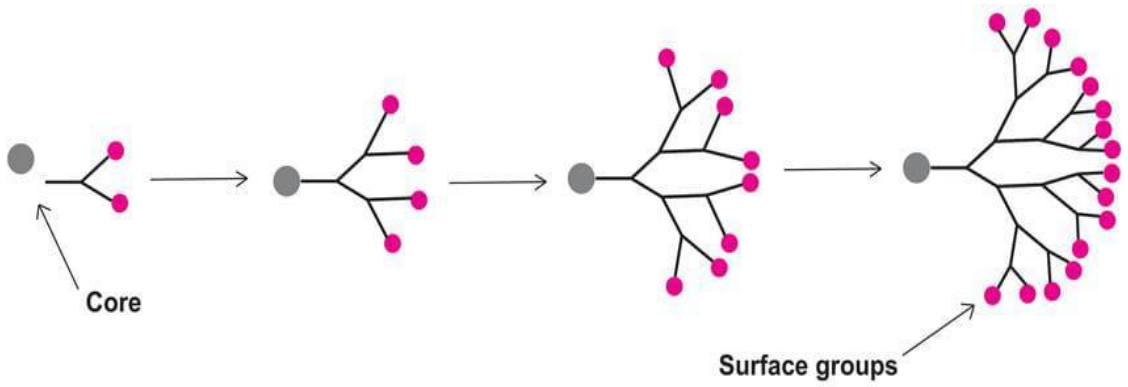

Figure 4: Synthesis by Divergent Method

2. Convergent Method

Convergent method of dendrimer synthesis was introduced by Frechet in year 1990. This method overcome the purity and structural defects issues of divergent synthesis. By convergent method symmetric and uniform dendrimer are synthesis but the overall yield is less. The yield is reduced for the uniformity of the purity as well as it is laboratory scale dendrimer synthesis. For large scale mostly divergent method is preferred.[24]

Convergent dendrimer growth starts at the dendrimer's surface and proceeds inward by progressively linking surface units. Once the growing segments reach a sufficient size, multiple units are attached to an appropriate core to form a complete dendrimer.[23]

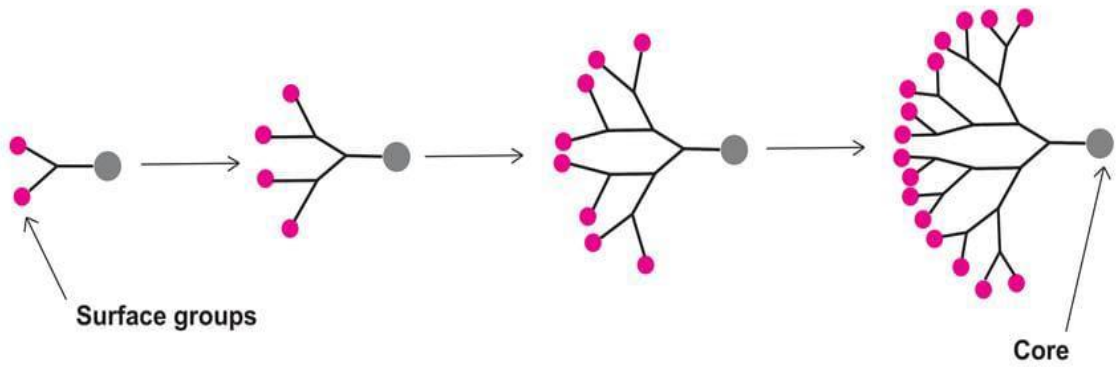

Figure 5: Synthesis by Convergent Method

3. Double Exponential or Mixed Growth

The Double Exponential and Mixed approach involves two monomers that undergo both convergent and divergent growth to form an orthogonally secure trimer. This trimer serves as an intermediate that can be reused in subsequent growth cycles, enabling the creation of large, complex dendrimers. The strength of double exponential growth lies in its efficiency, allowing the dendrimers to be built rapidly in fewer steps compared to traditional methods. This approach maximizes the precision and scalability of dendrimer synthesis while minimizing the number of steps required for constructing large, branched molecules.[15]

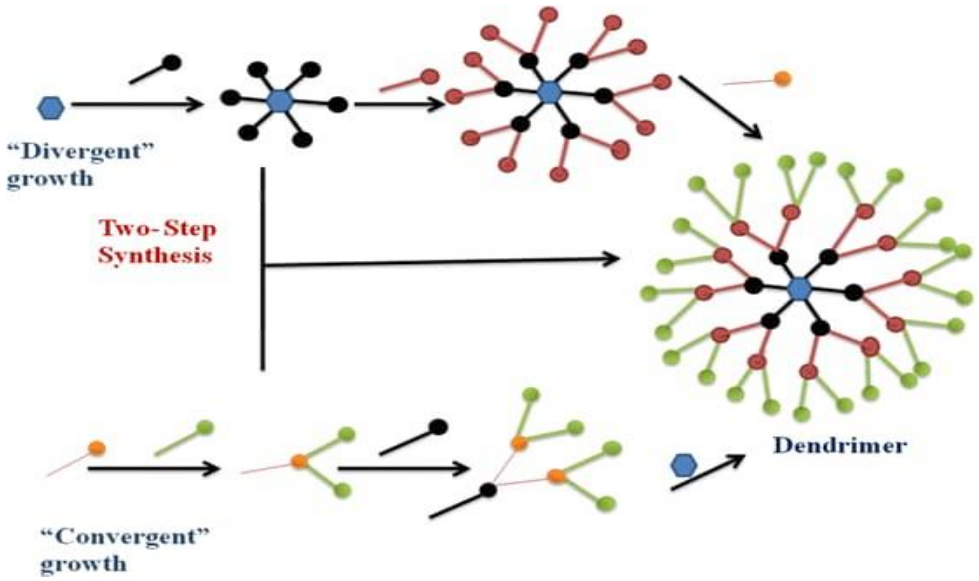

Figure 6: Synthesis of Dendrimer by Double Exponential or Mixed Growth Method

4. Hypercores and Branched Monomer Growth

To address the limitations of divergent and convergent methods, Hypercores and branched monomers were introduced.[25] This approach involves the pre-assembly of oligomeric species, which can then be linked together to form a dendrimer in fewer steps, resulting in higher yields with multiple branching. In this method, the core molecule reacts with one or more reagents, each containing at least one protected branching site, facilitating the formation of branched structures more efficiently.[26]

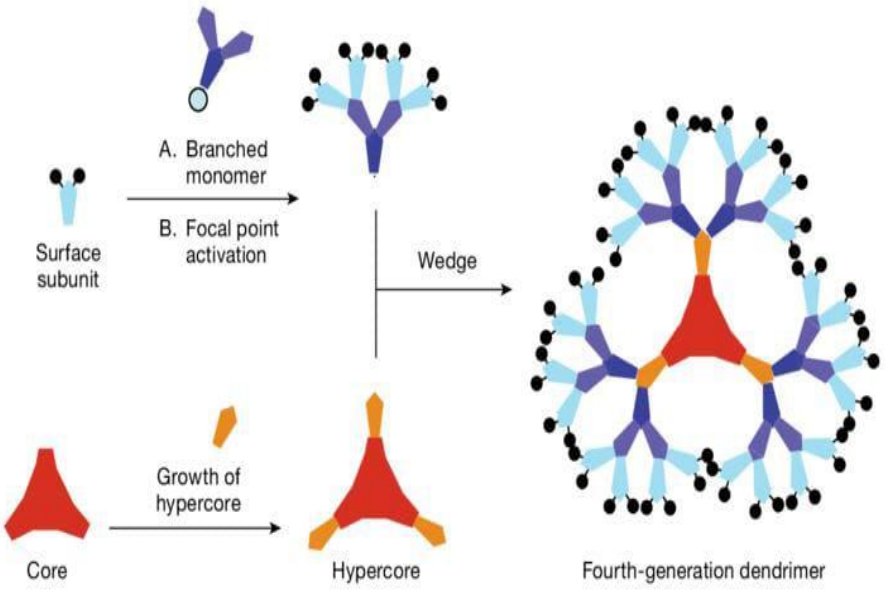

Figure 7: Synthesis of Dendrimer by Hypercores and Branched Monomer Growth Method

MECHANISM OF DRUG DELIVERY

Dendrimers are highly appealing for drug delivery due to their significant drug-loading capacity. Their well-defined three-dimensional structure and numerous surface functional groups allow for drug molecules to be either encapsulated within the dendrimer's interior or attached to its surface. They can serve as drug carriers by either encapsulating drugs or forming prodrugs through interactions with terminal functional groups, employing methods such as non-covalent encapsulation and covalent dendrimer-drug conjugates.[27]

1. Non-Covalent Drug Encapsulation

Dendrimers can encapsulate small organic molecules through non-covalent interactions, effectively trapping drugs within their architecture. This physical entrapment leverages the dendrimer's outer structure or the interactions between the dendrimer and the drug, allowing for controlled drug delivery. Initial studies investigated dendrimers as unimolecular micelles and "dendritic boxes" that could encapsulate drugs, including research that complexed DNA with Poly(amidoamine) (PAMAM) dendrimers for gene delivery and integrated hydrophobic drugs and dyes into the dendrimer cores. A significant advantage of these dendritic micelles over traditional polymeric micelles is their structural stability across different concentrations, due to the covalent bonding of hydrophobic segments.[28] For example, Jansen et al. successfully encapsulated rose bengal dye in Poly(propylene imine) (PPI) dendrimers, showcasing the stability of these dendritic boxes with bulky amino groups on their surfaces.[29]

2. Covalent Dendrimer - Drug Conjugates

Alternatively, dendrimers can form complexes with drug molecules via their multivalent nature, enabling drug attachment to their surface. These complexes can arise from electrostatic interactions or through covalent bonds formed directly or via linkers or spacers. Drugs that are ionizable can form stable complexes with the many ionizable terminal groups on dendrimers.[30] This method allows for precise tuning of drug loading based on the dendrimer generation and facilitates controlled drug release by incorporating degradable linkages between the dendrimer and drug. Various biologically active compounds, including drugs, antibodies and lipids, have been successfully conjugated to dendrimers. For example, drugs like naproxen and propranolol have been conjugated to poly(amidoamine) (PAMAM) dendrimers, resulting in enhanced solubility and improved release profiles compared to their unmodified forms. Additionally, many anticancer agents have been linked to dendrimers for targeted delivery, such as epirubicin conjugated with PEG (Polyethylene Glycol) dendrimers, which demonstrated improved therapeutic efficacy and stability.

Dendrimer-cisplatin complexes have shown increased solubility and reduced systemic toxicity, along with enhanced effectiveness against tumors. By carefully designing dendrimer synthesis, researchers can also attach both hydrophobic drugs and PEO (polyethylene oxide) moieties to surfaces in a controlled fashion, with aliphatic polyester dendrimers showing promise as backbones for developing anticancer drug conjugates.[31]

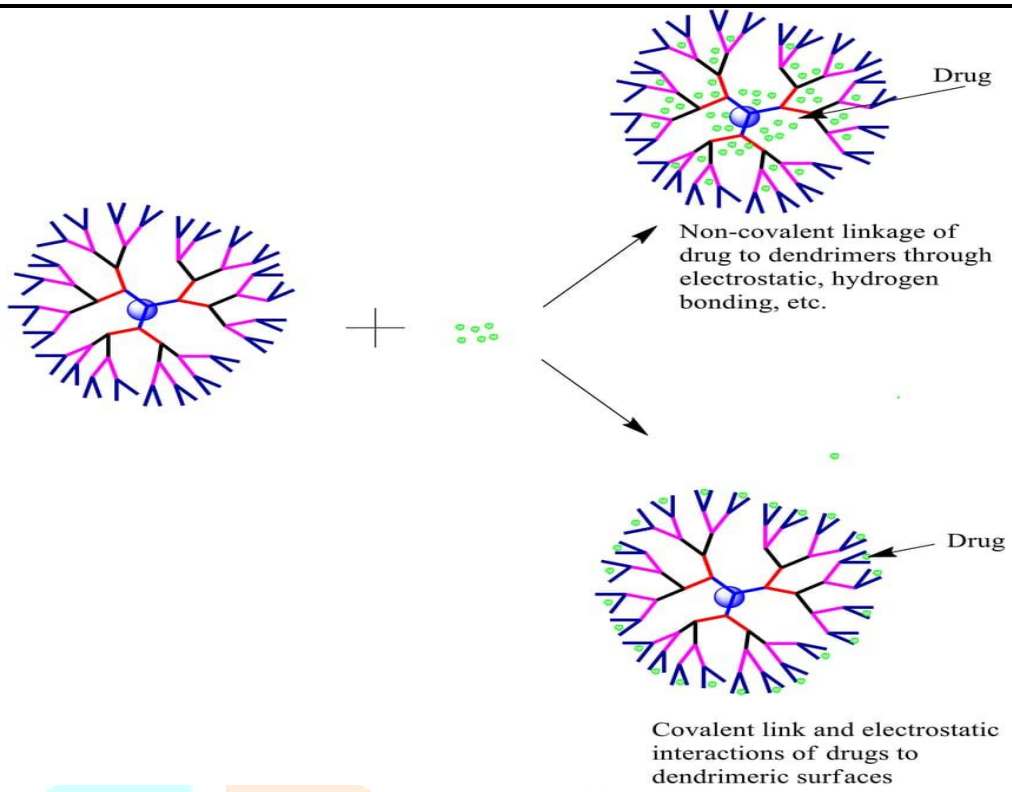

Figure 8: Different Type of Drug-Dendrimer Interaction

PROPERTIES OF DENDRIMERS

1. Size and Shape

Dendrimers exhibit enhanced physical and chemical properties owing to their unique molecular structure. Their shape varies with generation; lower-generation dendrimers typically adopt an open, planar, elliptical form, while higher-generation dendrimers tend to have a more compact, spherical shape. However, high-generation dendrimers often exhibit inherent structural defects during synthesis, such as incomplete reactions and steric hindrance. These issues can lead to missing repeating units, intramolecular cyclization, dimer formation and retro-michael reactions. Due to their nanoscale size and protein-like properties, dendrimers are sometimes referred to as artificial proteins.[32]

2. Solubility

Dendrimers typically exhibit better solubility in common solvents compared to linear polymers. Their solubility is influenced by several factors, including the type of peripheral functional groups, the nature of the repeating units and even the core structure. Dendrimers with hydrophilic end groups are soluble in water, while those with hydrophobic end groups tend to dissolve in non-aqueous solvents.[33]

3. Polyvalency

Polyvalency refers to the arrangement of reactive groups on the surface of a dendrimer nanostructure. This feature enables versatile functionalization, facilitating multiple interactions with biological receptor sites, such as in the development of antiviral drugs. Polyvalency is linked to the number of reactive sites on the

dendrimer's exterior, which can form connections with various materials of interest. Multivalency enhances interactions with biological targets, as most molecular interactions in biological systems occur through multivalent bonds.[34]

4. Monodispersity

The monodispersity means that the dendrimer has a well-defined molecular structure without any large individual variations. They are homogeneous due to their controlled synthesis and purification processes.[35]

5. Optimized Bio-distribution

By modifying surface groups, dendrimers can improve biodistribution, facilitate receptor-mediated targeting and allow for controlled drug release from their internal space.[36]

6. Low Viscosity

Low viscosity is a key characteristic of dendritic macromolecules. Dendrimers exhibit significantly lower viscosity in solution compared to linear polymers. While viscosity generally increases with the number of monomers, it tends to decrease in dendritic macromolecules after reaching a certain generation (usually around generation 4). Consequently, higher-generation dendrimers, which possess more functional groups, have a lower viscosity than their lower-generation counterparts. This behavior contrasts with linear polymers, where the inherent viscosity increases proportionally with molecular weight. The low viscosity of dendrimers is advantageous as it facilitates the formation of dendrimer-drug complexes and promotes faster drug release.[37]

7. Toxicity

Some dendrimer systems display very low toxicity levels with dendrimers carrying anionic groups being less toxic than those carrying cationic groups. Dendrimers may cause toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity. [38]

FACTOR AFFECTING DENDRIMERS

1. Effect of pH

The structural behavior of poly(amidoamine) (PAMAM) dendrimers in relation to pH, as demonstrated by molecular dynamics simulations, reveals distinct conformations. At low pH (below 4), the dendrimers exhibit an extended structure with a progressively hollow interior due to repulsion among the positively charged surface and interior amines, particularly as the generation number increases.[39]

At neutral pH, the dendrimers undergo back-folding, likely driven by hydrogen bonding between uncharged tertiary amines in the center and positively charged amines on the surface. When the pH exceeds 10, the dendrimers contract, achieving a more spherical (globular) form as the molecule's charge neutralizes, minimizing repulsive forces among the dendrimer arms and surface groups. This results in increased back-folding due to the weakened inter-dendron repulsions.[40]

2. Effect of Solvent

The ability of a solvent to solvate dendrimers is crucial for understanding their conformational states. Generally, dendrimers of all generations display increased backfolding when the solvent quality decreases. Lower-generation dendrimers, being more flexible, exhibit the greatest backfolding tendencies under poor solvation conditions compared to higher-generation ones. NMR studies of Poly(propylene imine) (PPI) dendrimers revealed that nonpolar solvents, like benzene, poorly solvate dendrimers, promoting intramolecular interactions and backfolding. Conversely, weakly acidic solvents such as chloroform can act as hydrogen donors to the interior amines of basic dendrimers like PPI, leading to extended conformations due to strong hydrogen bonding with the amines. Both experimental and theoretical studies of amino-terminated Poly(propylene imine) (PPI) and Poly(amidoamine) (PAMAM) dendrimers (which are polar) indicate that nonpolar aprotic solvents lead to higher molecular densities in the core due to backfolding, while polar solvents enhance solvation of the dendrimer arms, increasing molecular density on the surface. The backfolding of polar surface groups can expose more hydrophobic regions of the dendrimer, reducing overall surface polarity.[41]

3. Effect of Salt

Salt concentration plays a crucial role in the conformation of charged Poly(propylene imine) (PPI) dendrimers. In high ionic strength conditions, the added salt reduces electrostatic repulsion between charged segments, causing the dendrimer to adopt a contracted conformation and increased backfolding. This effect is similar to that observed under elevated pH or poor solvation conditions. In contrast, in low-salt environments, the reduced ionic shielding increases repulsive forces between the charged segments, promoting an extended conformation. This extended structure helps minimize charge repulsion by maximizing the distance between like charges, maintaining the dendrimer's stability.[39]

4. Effect of Concentration

In dendrimers with flexible structures, conformation is influenced not just by small molecules such as solvents, salts, or protons, but also by larger entities like other dendrimers or surfaces, which can significantly impact molecular density and conformation. Small angle X- ray scattering (SAXS) experiments performed on PPI dendrimer (G4, G5) in a polar solvent like methanol demonstrate that the molecular conformation of dendrimer upon increasing concentration becomes gradually more contracted. This molecular contraction may minimize the repulsive forces between the dendrimers molecule and increase the ability of the dendrimers to demonstrate a more tight intermolecular packing.[27]

ADVANTAGES OF DENDRIMERS

The following properties of the dendrimers make them an ideal carrier for drug delivery, therapy and diagnosis.

1. Targeted Drug Delivery

Dendrimers can be functionalized with specific ligands, allowing for precise targeting of diseased cells and tissues, thereby enhancing therapeutic efficacy while minimizing side effects.[42]

2. Controlled Release

The unique structure of dendrimers allows for a controlled and sustained release of drugs, leading to improved therapeutic outcomes and patient compliance.[43]

3. High Permeability

This characteristic enhances the intracellular transport of drugs. Dendrimers can effectively cross biological barriers, such as the blood-brain barrier and cell membranes. Their nanometer size range and uniformity facilitate their ability to traverse cell membranes while reducing the risk of unwanted clearance by organs like the liver or spleen.[44]

4. High Loading Capacity

Dendrimers structures can be used to load and store a wide range of organic or inorganic molecules by encapsulation and absorption on surface. Drug can get entrapped inside the internal cavities as well as electro statically in the surface of dendrimers.[45]

5. Low Polydispersity Index

They have lower polydispersity 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 entrapment of variety of drugs.[46]

6. High Uniformity and Purity

The synthesis method yields dendrimers with uniform size distributions, well-defined surface functionalities and minimal impurities. Monodispersed dendrimers enable precise targeted drug delivery.[47]

7. Low Toxicity

Most dendrimer systems exhibit low cytotoxicity but have good biodegradability. PEGylation of the dendrimer surface can enhance circulation time and further decrease toxicity.[48]

8. Low Immunogenicity

Dendrimers demonstrate low or negligible immunogenic responses when administered via injection or topical application. Unlike vesicular systems, which face issues like chemical instability, drug leakage, aggregation, fusion during storage, solubility in physiological environments and phospholipid lysis, dendritic systems do not encounter these challenges related to the purity of natural phospholipids.[49]

9. Sustained Effect

Dendrimers releases drug in a sustained manner. Poly(amidoamine) (PAMAM) dendrimers exhibited slower release, higher accumulation in solid tumors and lower toxicity. Conjugation with Polyethylene glycol on the surface of these nanocarriers avoids non-specific interaction with plasma proteins or engulfment. Increase in blood circulation time is essential to achieve desired clinical effect.[50]

10. High Stability

Dendrimers drug complex or conjugate shows better colloidal, biological and shelf-stability. Dendrimers have nanoscopic particle size range from 1-100nm, which makes them less susceptible for reticulum endothelium uptake.[51]

FUNCTIONALIZATION OF DENDRIMERS

Functionalization of dendrimer is the process of incorporating multiple active sites in dendrimers in order to create macromolecules with multifunctional architecture. Functionalized dendrimers also known as structurally controlled dendrimers have at least six well defined Nanoscale features known as Critical Nanoscale Design Parameters (CNDPs) such as size, shape, surface chemistry, flexibility, rigidity, architecture and elemental composition.[52]

1. Reducing Toxicity

To reduce toxicity and enhance biocompatibility, dendrimers can be functionalized with biocompatible molecules. Methods include adding biocompatible moieties to the core, using branched dendrimers, and surface modifications like acetylation, glycosylation, amino acids or peptides etc. These strategies improve drug loading, stability, biodistribution and reduce cytotoxicity.[53]

- **Acetylated Dendrimers**

The acetylation of dendrimers is another effective method of reducing their toxicity; this is because the acetyl group is conjugated with the terminal group, thus neutralizing the positive charges on the surface of the dendrimers. Acetylated dendrimers exhibit higher water solubility; this is important for drug development and bioapplications.[54]

- **Dendrimers Conjugated with Amino Acids or Peptide Groups**

Amino acids and peptides, naturally produced by the human body, are biocompatible and safe for use in human tissues. Dendrimers tagged with amino acids like phenylalanine and glycine have shown a significant reduction in toxicity, including cytotoxicity, hemotoxicity and immunogenicity. Amino acid conjugation is used to attach these molecules to dendrimers, enhancing their safety profile. Kono et al. synthesized PAMAM G 5.0 dendrimers conjugated with arginine, phenylalanine and leucine and compared their gene transfection efficiency. These amino acid-conjugated dendrimers demonstrated improved immunostimulatory capabilities.[55] And could serve as potential candidates for DNA vaccines due to their high transfection and targeting abilities.[56]

2. Improving Targetability

➢ **Folate-Conjugated Dendrimers**

Folic acid receptors are overexpressed in many types of tumor cells, such as those found in the kidney, lung, ovary, endometrium, colorectal, mammary, breast, testis, erythrocytes, neuroendocrine carcinomas and brain metastases. Thus, receptor-mediated endocytosis facilitates the penetration and uptake of folic acid-conjugated nanoparticles into tumor cells and increases targetability. In this sense, folic acid-conjugated nanocarriers might be effective in cancer-targeting therapies. Moreover, dendrimers that have been modified with folic acid on their surfaces may function effectively as a gene delivery agent, imaging agent and diagnostic agent.[57]

➢ **Antibody-Functionalized Dendrimers**

Antibody-functionalized dendrimers represent a novel strategy for targeted drug delivery, enabling the precise delivery of cytotoxic and other therapeutic agents to specific tissues. These antibodies help the immune system identify and target tumor cells that produce unique antigens. The antibody-conjugated dendrimers also interact with the blood vessels and tissues that sustain tumor growth, inhibiting the factors necessary for tumor development, a process known as the anti-angiogenic effect. Due to their low immunogenicity and poor water solubility, PAMAM dendrimers have proven to be highly effective carriers for antibodies, enhancing the delivery and effectiveness of cancer therapies.[58]

➢ **Carbohydrate-Engineered Dendrimers**

Glycodendrimers are dendritic structures containing carbohydrates, classified based on the carbohydrate distribution (center, base, surface). Cationic dendrimers coated with carbohydrates show reduced hemolytic toxicity, lower immunogenicity and improved drug delivery.[59] For example, Bhadra et al. successfully delivered primaquine phosphate to liver cells using galactose-conjugated dendrimers. Comparisons of galactose-coated PPI dendrimers with uncoated ones highlight enhanced efficacy and reduced hematological toxicity and cytotoxicity.[53]

APPLICATIONS OF DENDRIMERS

Specific properties such as unparalleled molecular uniformity, multifunctional surface and presence of internal cavities makes dendrimers suitable for a variety of high technology uses and are as follows:

1. Pharmaceutical Applications

➢ **Dendrimers in Transdermal Drug Delivery**

Dendrimers can enhance drug solubility and circulation time through transdermal formulations, capitalizing on their water solubility and biocompatibility. Their viscosity helps in handling concentrated formulations for these applications. The permeation of drugs like NSAIDs, such as ketoprofen and diflunisal, through the skin

can be improved when complexed with poly(amidoamine) (PAMAM) dendrimers. Using indomethacin as a model drug, poly(amidoamine) (PAMAM) dendrimers have been shown to enhance bioavailability in transdermal applications.[60]

- **Dendrimers in Ocular Drug Delivery**

Due to their nanoscale size, ease of preparation and ability to functionalize, dendrimers serve as effective vehicles for ophthalmic drug delivery. For example, poly(amidoamine) (PAMAM) dendrimers with carboxylic or hydroxyl surface groups enhance the residence time and bioavailability of pilocarpine in the eye. Additionally, phosphorus-containing dendrimers with quaternary ammonium cores and terminal carboxylic groups have been successfully utilized for delivering carteolol.[61]

- **Vaccine Development and Delivery**

Dendrimers hold promise in vaccine development and delivery due to their unique properties, which can enhance antigen stability, promote immune responses, and enable targeted delivery.[62] Encapsulation of antigens within dendrimers protects them from degradation and facilitates controlled release, prolonging their exposure to the immune system. Furthermore, dendrimers can be functionalized with targeting ligands to direct vaccine components to specific immune cells or tissues, enhancing vaccine efficacy and reducing off-target effects.[63]

- **Dendrimers in Pulmonary Drug Delivery**

Dendrimers, due to their distinct structural characteristics and adjustable surface functionalities, have become adaptable carriers for pulmonary drug delivery, providing benefits like enhanced drug solubility, prolonged release, and precise delivery to targeted areas of the lungs. Dendrimers are capable of engaging with mucosal surfaces in the lungs and breaking down the mucus barrier, which aids drug absorption into the deeper tissues. The compact dimensions and elevated surface to volume ratio of dendrimers facilitate effective movement through the mucus layer, improving drug uptake and spread in the lungs. Modifying the surface of dendrimers with targeting ligands enables precise drug delivery to specific lung areas or cellular receptors. This allows for targeted drug delivery, decreasing systemic exposure and lowering off-target effects.[64]

- **Drug Delivery to the Central Nervous System (CNS)**

Dendrimers have emerged as a promising approach for drug delivery to the central nervous system (CNS) due to their unique characteristics. One of the major obstacles in CNS drug delivery is the blood-brain barrier (BBB), which limits the entry of many therapeutic agents because of its tight junctions and efflux pumps. However, dendrimers, with their precisely controlled nanoscale size, can potentially navigate these tight junctions more effectively. Moreover, the surface of dendrimers can be modified with various ligands, such as peptides or antibodies, which can specifically bind to receptors or transporters on the BBB endothelial cells, thereby enhancing their uptake into the brain.[65]

➢ **Dendrimers in Targeted Drug Delivery**

Dendrimers have garnered significant interest as potential drug delivery vehicles because of their unique properties. They can deliver drugs by either encapsulating them within their internal voids or by attaching them to surface functionalities. These features make dendrimers particularly suitable for targeted drug delivery systems. For instance, poly(amidoamine) (PAMAM) dendrimers can be conjugated with folic acid for targeting tumor cells and fluorescein isothiocyanate for imaging purposes.[66]

➢ **Dendrimers in Targeted Gene Delivery**

Dendrimers are extensively used as non-viral vector for gene delivery. They can work as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Various polyatomic compounds such as PEI, poly(lysine) and cationic have been utilized as non-viral gene carrier. Poly(amidoamine) (PAMAM) dendrimers have also been tested as genetic material carriers.[67] Cationic dendrimers, Poly(propylene imine) (PPI) dendrimers deliver genetic materials into cells by forming complexes with negatively charged genetic materials through electrostatic interaction. Furthermore, dendrimers are non-immunogenic and are thus uniquely suited as carrier structures for drugs or bioactive molecules without degradation in immune system.[67]

➢ **Dendrimer in Oral Drug Delivery**

Oral drug delivery remains the preferred route for administering pharmaceuticals due to its convenience, patient compliance, and non-invasiveness. However, challenges such as low bioavailability, degradation in the gastrointestinal (GI) tract, and poor intestinal absorption limit the efficacy of orally administered drugs. Dendrimers can encapsulate hydrophobic drugs within their interior, enhancing their solubility in aqueous media and protecting them from enzymatic degradation in the GI tract. Surface modification of dendrimers with stabilizing agents further improves the stability of encapsulated drugs, ensuring their preservation during transit through the acidic environment of the stomach.[68]A study done by researcher Kolhe et al. who synthesized a dendrimer-ibuprofen complex, which results in better efficacy and pharmacological activity compared to pure ibuprofen.[69]

2. Therapeutic Applications

➢ **Dendrimers in Anticancer Drug Delivery**

One of the primary uses of dendrimers is as vehicles for delivering various anticancer drugs. Their structure and adjustable surface functionalities enable the encapsulation or conjugation of multiple therapeutic agents, making them ideal carriers for anticancer treatments. For example, a dendritic nano-formulation featuring doxorubicin covalently linked via a hydrazone bond to a high molecular weight three-arm polyethylene oxide has shown reduced cytotoxicity in vitro. To enhance the efficacy of doxorubicin, Lai et al. employed photochemical internalization (PCI) technology for the targeted delivery of membrane-impermeable macromolecules from endocytic vesicles into the cytosol. Additionally, many researchers have investigated the potential of incorporating cisplatin into dendrimer formulation.[61]

➢ **Dendrimers for Boron Neutron Capture Therapy**

The radiation energy produced from the interaction of low-energy thermal neutrons with atoms has been effectively utilized for the selective destruction of tissue. Dendrimers present an intriguing option as boron carriers due to their well-defined structure and multivalency.[70]

➢ **Brain Tumor Imaging**

Dendrimers show considerable potential in brain tumor imaging due to their distinct properties and versatile functionality. A study by Khan et al. highlighted that when dendrimers are linked to nanoparticles, they can serve as highly efficient contrast agents for various imaging techniques, including magnetic resonance imaging (MRI), computed tomography (CT), and fluorescence imaging. Similarly, Rodríguezerve Galvan et al. demonstrated that gadolinium chelated diagnostic agents are highly effective in tumor imaging when used as contrast agents. Dendrimer-linked nanoparticles offer several key advantages in brain tumor imaging. Their small size and the ability to precisely control surface chemistry allow them to penetrate the blood-brain barrier (BBB), a significant challenge in brain tumor diagnosis and treatment. By crossing the BBB, these nanoparticles can selectively accumulate at the tumor site, thereby improving the contrast between healthy brain tissue and tumor tissue.[71]

3. Diagnostic Applications

➢ **Imaging Agents**

Dendrimers can be modified with imaging probes like fluorophores, radioisotopes, or magnetic nanoparticles. These dendrimer-based imaging agents help visualize specific tissues, organs, or biological processes using imaging techniques such as fluorescence imaging, positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI) or computed tomography (CT). By targeting specific biomarkers or molecules associated with diseases.[72]

➢ **Contrast Agents**

In medical imaging, contrast agents are used to improve the visibility of targeted structures or tissues. Dendrimers can function as efficient contrast agents because they can carry large amounts of imaging agents. Additionally, dendrimers can be designed to specifically target certain cells or tissues, enhancing contrast and diagnostic accuracy. For instance, dendrimer-based MRI contrast agents can be tailored to accumulate in tumor tissues, improving the detection of cancerous lesions.[71]

➢ **Biosensors**

Dendrimers are utilized in the creation of biosensors devices designed to detect and measure specific biomolecules or analytes. Dendrimers can serve as frameworks for attaching sensing components such as antibodies, enzymes, nucleic acids, or receptors. These components interact with target analytes, producing measurable signals such as fluorescence, electrochemical changes or surface plasmon resonance (SPR).

Dendrimer-based biosensors are highly sensitive, selective and provide rapid detection, making them useful for diagnosing diseases, tracking therapeutic responses or identifying environmental pollutants.[73]

➢ **Dendrimers as Molecular Probes**

Dendrimers are promising candidates as molecular probes due to their unique structure and properties. Their large surface area and high density of surface functionalities make them ideal for immobilizing sensor units, enabling efficient creation of integrated molecular probes.[74]

CHALLENGES AND LIMITATIONS

Dendrimer-based drug delivery systems have shown promise in enhancing therapeutic efficacy, but several challenges and limitations hinder their widespread clinical application.

1. Toxicity

Dendrimers have shown great promise as nanocarriers in medical applications, but understanding their toxicity is crucial for their safe use. The toxic effects of dendrimers are closely tied to their structural characteristics. Due to their nanoscale size, dendrimers can interact with various cellular components, including the plasma membrane, organelles (like endosomes, mitochondria, and nuclei), proteins (such as enzymes), heavy metals, ions, vitamins, and nucleic acids.[75] These interactions can result in membrane disruption, the generation of reactive oxygen species (ROS) and the release of cytokines, potentially leading to cell damage and death.[76]

2. Complex Synthesis

The synthesis of dendrimers is typically intricate and involves multiple steps of chemical reactions, which increases production costs. Achieving precise control over size, shape and surface functionality requires advanced synthetic techniques, contributing to scalability issues for large-scale manufacturing. This complexity also translates into longer production times and higher costs, which can hinder the commercial viability of dendrimer-based formulations.[77]

3. Stability

Dendrimers may face stability concerns in vivo, including rapid degradation or premature drug release. Their small size and surface properties can influence their biodistribution and cause rapid clearance from the body, reducing their therapeutic efficacy.[78]

FUTURE PROSPECTIVES

Dendrimer-based drug delivery systems have garnered significant attention in recent years due to their unique architecture, precision in drug release, and potential to enhance therapeutic efficacy. However, future advancements hold the potential to further revolutionize the field of drug delivery. Key areas for future development include innovations in dendrimer synthesis, advanced functionalization strategies, and the integration of dendrimers with nanotechnology and other drug delivery platforms.

1. Innovations in Dendrimer Synthesis

One significant innovation in dendrimer synthesis is the development of biodegradable dendrimers. Traditional dendrimers, while effective, often accumulate in the body due to their non-biodegradable nature, raising concerns about long-term toxicity. To address this, researchers are focusing on designing dendrimers made from biodegradable and biocompatible materials like polyesters or poly(amidoamine) derivatives. These biodegradable dendrimers are expected to break down into non-toxic metabolites after performing their drug delivery functions, significantly improving their safety profile and environmental impact.

2. Advanced Functionalization Techniques

Advances in functionalization will allow dendrimers to carry multiple targeting agents like antibodies or peptides enabling more precise delivery of drugs to specific cells or tissues. Researchers are also working on stimuli-responsive dendrimers, which release drugs in response to specific triggers (e.g., pH changes or enzymes), ensuring that drugs are only released at the site of disease. This could significantly reduce side effects and improve treatment outcomes.

3. Integration with Nanotechnology and Other Platforms

Combining dendrimers with other advanced drug delivery systems, such as liposomes or nanoparticles, could improve the stability, solubility, and targeting of drugs. This integration has the potential to enhance the effectiveness of dendrimers in applications like gene therapy, cancer treatment, and personalized medicine.

CONCLUSION

Dendrimer drug delivery systems offer significant advantages in improving drug efficacy and precision. Their unique, highly branched structure allows for efficient drug encapsulation, including both hydrophobic and hydrophilic compounds, enhancing bioavailability and therapeutic effectiveness. Dendrimers enable controlled and sustained drug release, which helps in reducing side effects and improving patient outcomes. Additionally, their surface can be easily modified to target specific cells or tissues, making them highly suitable for targeted therapy, including cancer and gene delivery. Dendrimers also allow for the simultaneous delivery of multiple therapeutic agents, enabling combination treatments. Their versatility, ability to improve drug solubility, and targeted delivery capabilities position dendrimers as a promising platform in modern drug delivery systems. As research progresses, dendrimers continue to show great potential in revolutionizing drug delivery, offering safer and more effective treatment options for a variety of disease.

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