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DENDRIMER-BASED NANOCARRIERS: A REVOLUTIONARY APPROACH IN CANCER THERAPY

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ABSTRACT

Cancer, a deadly disease, has experienced a transformative shift in treatment approaches with the integration of nanotechnology into medicine and diagnostics. Among the various nanocarriers, dendrimers have emerged as a promising tool for cancer therapy, including chemotherapy, gene therapy, and drug delivery. These unique supramolecular dendritic polymers offer several advantages, such as improved solubility and bioavailability, making them highly effective in delivering therapeutic agents. Despite significant advancements, one of the major challenges in cancer treatment remains the development of multidrug resistance to chemotherapeutic agents. However, dendrimers, with their three-dimensional, hyperbranched, globular nanostructures, hold great potential to overcome this hurdle by enhancing drug delivery and therapeutic efficacy.

KEYWORDS: Cancer, Dendrimers, Nanocarrier, Theragnostic, Cancer Therapy, PAMAM, Drug Delivery etc.

INTRODUCTION

Cancer is a complex disease characterized by the uncontrolled growth and spread of abnormal cells within the body. This malignant behavior occurs when certain cells acquire the ability to proliferate uncontrollably, forming tumors that can invade surrounding tissues and potentially metastasize to distant organs. The spread of cancer cells throughout the body is facilitated by the blood and lymphatic systems, enabling these cells to colonize new areas and form secondary tumors.

At the molecular level, cancer arises from specific changes or mutations in genes, which are

the fundamental units of heredity. These genes, composed of DNA, are organized into tightly packed structures known as chromosomes. Under normal circumstances, genes regulate cell growth, division, and death, ensuring that cells function properly. However, when these genes are altered, either by environmental factors, lifestyle choices, or inherited predispositions, they can trigger the abnormal behavior of cells, leading to the development and progression of cancer. These genetic mutations can disrupt the normal regulatory mechanisms of the cell, allowing cancer cells to evade apoptosis (programmed cell death), resist growth suppression, and continuously divide without control.[1-3]

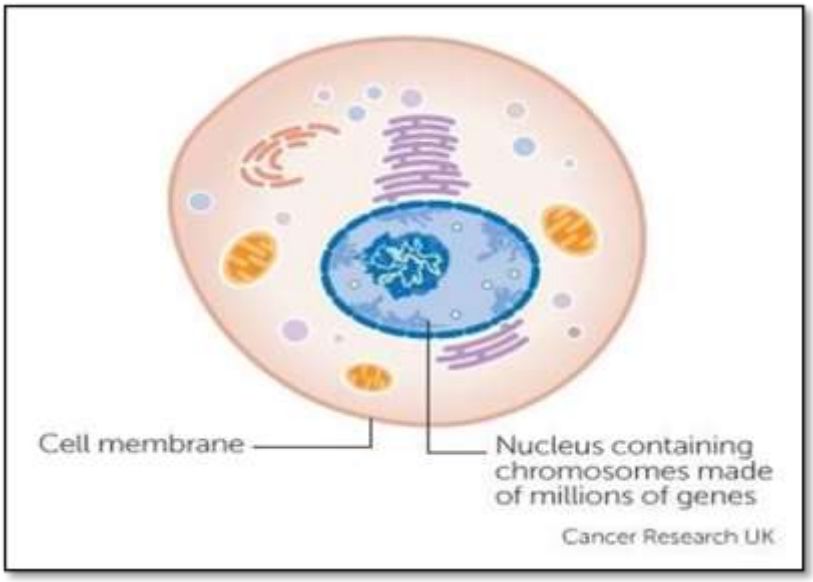

Figure 1: How does starts in Cancer.[37]

Type of Cancer

Cancer is a broad term encompassing a wide range of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. These malignant cells can invade nearby tissues, and in many cases, they can metastasize, or spread, to other parts of the body through the blood and lymphatic systems. Cancer can develop in almost any part of the body, and the specific type of cancer is determined by the origin of the malignant cells.

There are several main types of cancer, each named based on the type of cell or tissue in which it begins. For instance, carcinomas originate in epithelial cells that line the body's surfaces and internal organs, making them the most common type of cancer. Sarcomas arise from connective tissues like bone and muscle, while leukemias and lymphomas develop in blood-forming tissues and the immune system, respectively. Other types, such as melanomas, germ cell tumors, and central nervous system cancers, affect specialized cells and tissues.

Each type of cancer behaves differently, requiring tailored approaches to treatment and management. Understanding the various types of cancer is crucial for developing effective therapies and improving patient outcomes.

Table 1: The different types of cancer.

Type of Cancer	Description	Common Locations	Examples
Carcinoma	Cancers that originate in the epithelial cells that line the body's internal and external surfaces. They are the most common type of cancer.	Skin, lungs, breasts, pancreas, and other organs	- **Adenocarcinoma**: Arises in glandular tissues (e.g., breast cancer). - **Squamous Cell Carcinoma**: Arises in squamous cells (e.g., skin cancer).
Sarcoma	Cancers that originate in the connective or supportive tissues, such as bones, muscles, cartilage, and fat.	Bones, muscles, fat, cartilage, blood vessels	- **Osteosarcoma**: Cancer of the bone. - **Liposarcoma**: Cancer of fat cells. - **Chondrosarcoma**: Cancer of cartilage.
Leukemia	Cancers that originate in the blood-forming tissues, such as the bone marrow, and result in the production of abnormal white blood cells.	Blood and bone marrow	- **Acute Lymphoblastic Leukemia (ALL)**: Rapidly progressing cancer of immature white blood cells. - **Chronic Myeloid Leukemia (CML)**: Slower-progressing cancer.
Lymphoma	Cancers that originate in the lymphatic system, which is part of the body's immune system.	Lymph nodes, spleen, thymus, bone marrow	- **Hodgkin Lymphoma**: Characterized by the presence of Reed-Sternberg cells. - **Non-Hodgkin Lymphoma**: More diverse group of lymphatic cancers.
Melanoma	A type of cancer that develops in melanocytes, the cells responsible for producing the pigment melanin in the skin.	Skin (most common), eyes, and other pigmented tissues	- **Cutaneous Melanoma**: Skin melanoma. - **Ocular Melanoma**: Melanoma in the eye.
Myeloma	A type of cancer that originates in the plasma cells of the bone marrow. It can disrupt the production of normal blood cells and weaken bones.	Bone marrow, bones (spine, skull, pelvis, ribs)	- **Multiple Myeloma**: Most common form, affecting multiple bones.
Central Nervous System (CNS) Cancers	Cancers that begin in the tissues of the brain and spinal cord.	Brain and spinal cord	- **Glioma**: Originates in glial cells. - **Medulloblastoma**: Common in children, originating in the cerebellum.
Germ Cell Tumors	Cancers that originate in the cells that give rise to sperm or eggs.	Testicles, ovaries	- **Testicular Cancer**: Cancer in the testicles. - **Ovarian Germ Cell Tumor**: Cancer in the ovaries.

Nanocarriers Used in Cancer Therapy

Nanocarriers in cancer therapy have shown remarkable potential due to their ability to

improve drug delivery systems, enhance bio-medicine applications, and provide controlled drug release.[29-30]

Fonctions of Nanocarriers

Nanocarriers play a critical role in enhancing the effectiveness and safety of drug delivery, particularly in cancer therapy. One of their primary functions is the encapsulation of functional organic solutes, such as poorly water-soluble drugs. By encapsulating these drugs, nanocarriers significantly improve their solubility and bioavailability, ensuring that a higher concentration of the drug reaches its intended target. Additionally, nanocarriers protect drugs from environmental factors that can lead to degradation, thereby enhancing the stability and shelf life of these therapeutic agents.

Nanocarriers are often modified on their surface to further optimize their performance. Hydrophilic coatings, for instance, can be applied to enhance the distribution of nanocarriers in the aqueous phase, ensuring better circulation within the body. Amphiphilic surfactants can also be used to improve the solubility and distribution of insoluble organic solutes, making it easier for these drugs to reach their targets.

In terms of pharmacokinetics, nanocarriers offer significant advantages. They protect medications from enzymatic degradation, thereby reducing the breakdown of the drug before it can exert its therapeutic effect. Furthermore, by reducing renal clearance, nanocarriers extend the circulation time of drugs in the bloodstream, prolonging their half-life and allowing for sustained therapeutic action. This also facilitates controlled and sustained release of anticancer drugs, ensuring a steady concentration of the drug over an extended period.

One of the most critical functions of nanocarriers is their ability to deliver drugs directly to targeted cancer cells. This targeted drug delivery enhances the therapeutic efficacy of cytotoxic drugs, allowing them to more effectively kill cancer cells. Moreover, by concentrating the drug at the site of the tumor, nanocarriers minimize the exposure of healthy tissues to the cytotoxic effects, thereby reducing side effects and improving the overall safety of the treatment. This combination of targeted delivery and controlled release makes nanocarriers a powerful tool in the fight against cancer.

Types of Smart Nanocarriers

Liposomes

- Spherical vesicles composed of lipid bilayers.
- Effective in encapsulating both hydrophilic and hydrophobic drugs.
- Can be functionalized with ligands for targeted delivery.

Polymeric Nanoparticles

- Made from biodegradable polymers like PLGA (polylactic-co-glycolic acid).
- Offer controlled drug release and high stability.
- Suitable for both systemic and localized drug delivery.

Dendrimers

- Highly branched, star-shaped polymers with a high degree of surface functionality.
- Capable of carrying multiple drug molecules.
- Provide precise control over drug release kinetics.

Gold Nanoparticles (AuNPs)

- Biocompatible and easily functionalized with various biomolecules.
- Used in drug delivery, imaging, and photothermal therapy.

Magnetic Nanoparticles

- Composed of magnetic materials like iron oxide.
- Can be guided to tumor sites using external magnetic fields.
- Useful in hyperthermia treatment and as MRI contrast agents.

Carbon Nanotubes (CNTs)

- Cylindrical structures with high surface area.
- Capable of carrying large amounts of drugs.
- Used for targeted drug delivery and thermal ablation therapy.

Quantum Dots (QDs)

- Semiconductor nanoparticles with unique optical properties.
- Used in bio-imaging and as carriers for targeted drug delivery.

Applications in Cancer Therapy

- **Targeted Drug Delivery**

Nanocarriers are designed to target cancer cells specifically, reducing systemic toxicity and improving therapeutic outcomes.

- **Bio-Imaging**

Nanoparticles like quantum dots and gold nanoparticles enhance imaging techniques, allowing for better diagnosis and monitoring of cancer.

- **Controlled Drug Release**

Smart nanocarriers release drugs in a controlled manner, maintaining therapeutic levels of the drug over extended periods.

- **Theragnostic**

Combining therapy and diagnostics, nanocarriers enable simultaneous treatment and monitoring of cancer progression.

Nanocarriers represent a significant advancement in cancer therapy, offering solutions to overcome the limitations of traditional drug delivery methods. By enhancing the solubility, stability, and targeting of anticancer drugs, they hold the promise of effective and less toxic cancer treatments.[31]

Dendrimer

Dendrimer is the nanoscience is an emerging field that deals with interactions between molecules cells & engineered substances such as molecular fragments, atoms & molecules.
Cancer is a disease that affects millions of Americans in all groups and both sexes. Dendrimers are repeatedly branched molecules the huge number of papers on dendritic architectures such as dendrimers, dendronized, hyperbranched.

Dendrimers have often been referred to as the "Polymers of the 21st century" dendrimer chemistry was first introduced in 1978 by fritz Vogtle & co-workers.1 He synthesized the first cascade molecules. In 1985 Donald A. Tomalin, synthesized the first family of dendrimers.[2]

The word "Dendrimer" originated from two words, the Greek Word Dendron, meaning tree & meres meaning part. Dendrimers have stimulated wide interest in the field of chemistry &

biology.[2]

Structure of Dendrimer

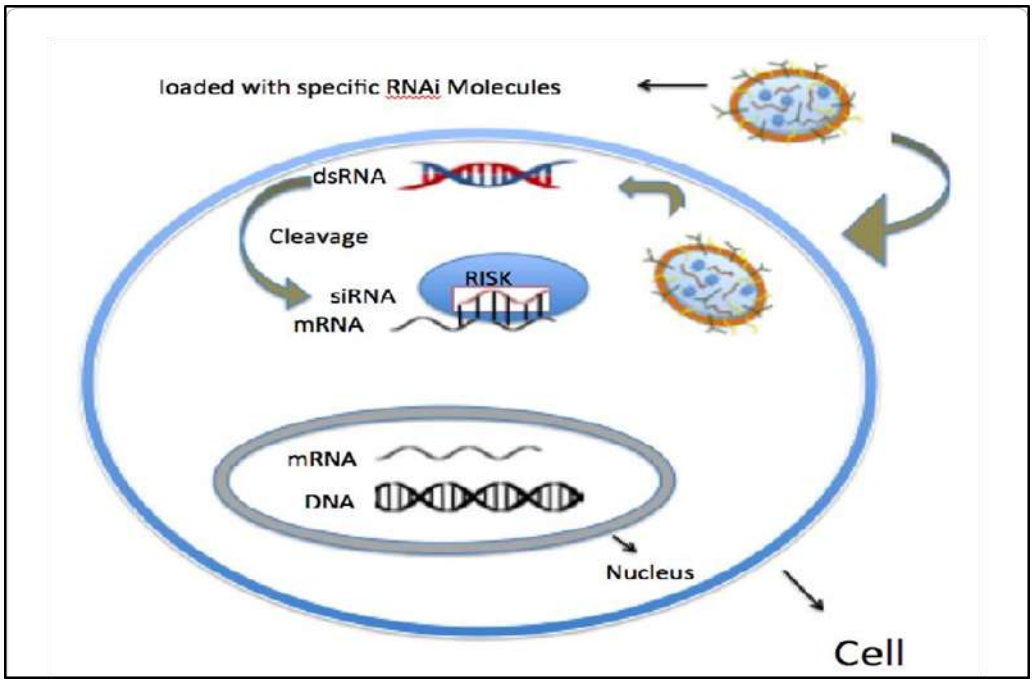

Figure 2: Structure of Dendrimer.[38]

Structure and chemistry

Dendrimers are highly structured macromolecules characterized by a central core from which successive layers or generations of branches, known as dendrons, extend outward. This unique architecture allows dendrimers to achieve a high degree of control over size, shape, and functionality, which is not typically possible with linear polymers.

There is ongoing debate within the scientific community regarding the exact structure of dendrimers. One major point of contention is whether dendrimers are fully extended with their branches maximizing surface density, or if their end-groups fold back, potentially creating a densely packed interior.

The ability to precisely control dendrimer synthesis is a significant advantage over conventional polymers. This control enables the production of nearly monodisperse (uniform in size), globular molecules with a large number of peripheral functional groups. These peripheral groups are positioned at the outermost layers of the dendrimer, offering numerous sites for interactions with other molecules or surfaces.[8-10]

For example, Figure likely illustrates the structure of some dendrimer repeat units, such as the

1,3-diphenylacetylene unit developed by Moore. This unit serves as an example of how dendrimers can be structured with defined repeat units, emphasizing their controlled and predictable synthesis compared to linear polymers.

In summary, dendrimers represent a class of macromolecules with a unique architecture that allows for precise control over their size, shape, and functional groups. The ongoing debate about their structure reflects their complex nature and the potential variability in how dendrimers can be synthesized and structured.[11-14]

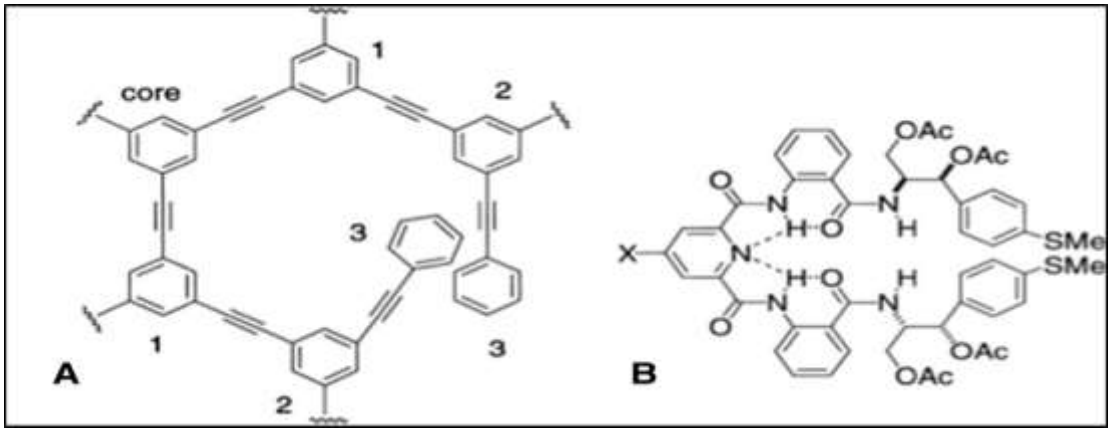

Figure 3: Types of Dendrimer.[36]

(A)Dendrimer consisting of phenyl acetylene subunits

1. Phenyl acetylene dendrimer: These dendrimers are characterized by their core made up of phenyl acetylene units. Dendrimers are highly branched molecules with a tree-like structure, where each generation (layer) adds more branches to the previous one. In your description.

"Third-generation different arms may dwell in the same space": This suggests that at the third generation, the branches (arms) of the dendrimer are close together in space.

"Fourth-generation layer potential overlaps with the second-generation layer": This indicates that the branches or layers of the fourth generation are spatially close to the layers of the second generation, potentially leading to interactions or overlaps.

This type of dendrimer structure is known for its precise architecture and potential applications in materials science, drug delivery, and nanotechnology.

(B)Parquette-type dendrons

1. Parquette-type dendrons: These dendrons are a specific type of dendritic structure designed by Professor Jon A. Parquette. Key characteristics include.

Chirality: The dendrons are chiral, meaning they exist in both left-handed and right-handed forms.

Non-racemic: Refers to the dendrons not being a racemic mixture (equal amounts of left- and right-handed forms).

Intramolecular folding driven by hydrogen bonding: The structure of these dendrons allows for internal folding due to hydrogen bonding interactions, which can influence their physical and chemical properties. These dendrons are notable for their potential applications in supramolecular chemistry, where their controlled folding and chiral nature can be advantageous.[14-16]

Phenyl acetylene dendrimers, characterized by their branching with phenyl acetylene subunits. Arquette-type dendrons, which are chiral, non-racemic, and feature intramolecular folding driven by hydrogen bonding. These types of dendrimers and dendrons have diverse applications across various fields due to their unique structures and properties.

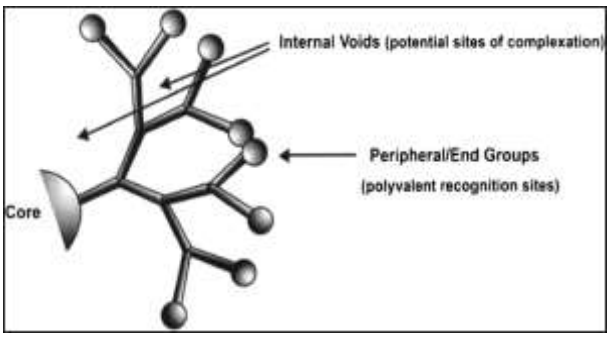

Figure 4: Main parts of Dendrimer.[36]

Some key terms and abbreviations commonly used in dendrimer chemistry[17-22]

- **Generation (G):** Refers to the number of layers or generations of branches emanating from the core of a dendrimer. Higher generations indicate more layers of branches.
- **Core:**–The central structure from which branches emanate in a dendrimer. It can vary widely depending on the type of dendrimer.
- **Branches or Dendrons:** The repeated units or arms that extend outward from the core in

a dendrimer structure.

- **Periphery or Surface Groups:** Functional groups located at the outermost layer (periphery) of a dendrimer. These groups can determine the dendrimer's solubility, reactivity, and interactions with other molecules.
- **Dendritic Pores:** Cavities or spaces within a dendrimer structure that can encapsulate guest molecules. These pores are often utilized in drug delivery applications.
- **Dendrimer Terminal Groups:** Functional groups located at the ends of dendrimer branches. They can play a crucial role in dendrimer conjugation and interactions with target molecules.
- **Divergent Synthesis:** A method of dendrimer synthesis where branches are sequentially added from a central core outward.
- **Convergent Synthesis:** A method of dendrimer synthesis where smaller dendron fragments are synthesized separately and then combined to form the final dendrimer structure.
- **Dendrimer PEGylation**: Attachment of polyethylene glycol (PEG) chains to dendrimers to enhance their solubility, stability, and biocompatibility.
- **Grafting:** Attachment of functional groups or molecules onto dendrimer branches or surface groups to modify dendrimer properties or enable specific interactions.
- **Dendrimer Toxicity**: Investigation of potential adverse effects of dendrimers on biological systems, crucial for biomedical applications.

These terms and abbreviations provide a concise way to describe the complex chemical events and structural features of dendrimers, facilitating communication and research in dendrimer chemistry and applications.

Classification of Dendrimer

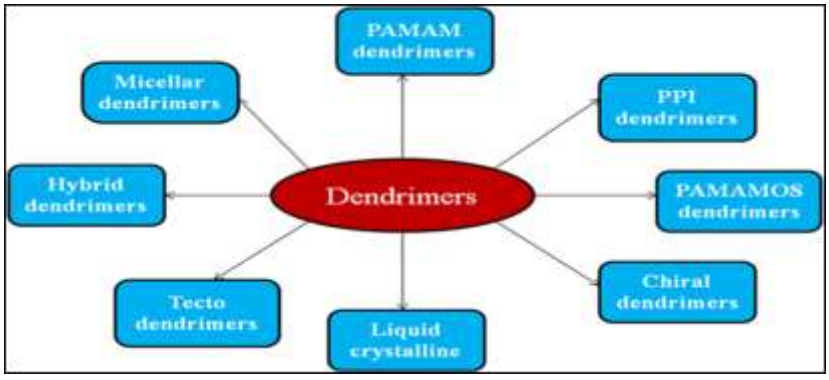

Figure 5: Classification of Dendrimer.[35]

Applications of Dendrimers

Dendrimers are highly branched, star-shaped macromolecules with applications across various fields, are as follows.

- **Biomedical Study**

Dendrimers are utilized as analogs to proteins, enzymes, and viruses. They are used to focus on target cells and are conjugated to host dendrimer cells. For example, poly(amidoamine) (PAMAM) dendrimers are used in this capacity.[23]

- **Magnetic Resonance**

Dendrimers improve the contrast in magnetic resonance imaging (MRI). Metallic dendrimers serve as MRI contrast agents.

- **Bio mimics**

Dendrimers mimic various biomolecules and create a microenvironment similar to natural biological systems.

- **Solubility Enhancement**

Dendrimers enhance the solubility of poorly soluble drugs, increasing their bioavailability.

- **Stability Enhancement**

Dendritic formulations stabilize ingredients within the core, providing dynamic internal cavities that protect neutral molecules and ions from degradation.[24]

- **Targeted Delivery**

Dendrimers facilitate site-specific drug delivery by targeting ligands conjugated to their surface.

- **Dummy and Carrier for Formulations**

Due to their uniform size, dendrimers can cross cell membranes, aiding various pharmacological activities.

- **Nanoparticles**
- PAMAM dendrimers act as nanoparticles due to the tertiary amine groups at their branching points. Metal ions are form complexes with the dendrimers and are reduced to form encapsulated nanoparticles.

- **Nanodrugs**

Dendrimeric formulations serve as nanodrugs. For example, propylene (PPL) dendrimers with sulfonated naphthyl groups are antiviral, while those with tertiary alkylammonium groups are antibacterial. Chitosan dendrimer hybrids also have antibacterial properties.

- **Hydrogel for Ocular Drug Delivery**

Dendrimeric hydrogels are cross-linked networks that swell in aqueous solutions. With added polyethylene glycol groups, they are used in cartilage tissue production, sealing ophthalmic injuries, and targeted drug delivery.

Transdermal Drug Delivery

Dendrimers enhance solubility and plasma circulation in transdermal formulations. PAMAM dendrimers form complexes with nonsteroidal anti-inflammatory drugs, enhancing skin permeation, as seen with indomethacin.

These benefits contribute to the rapid synthesis and diverse applications of dendrimers in fields such as catalysis, electronics, sensing, nanoengineering, diagnostics, and drug and gene delivery. Examples of dendrimers with these properties include PAMAM, poly (propylene imine) (PPI), poly(L-lysine) (PLL), and triazene-based dendrimers.[25-26]

Properties of Dendrimers

- Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers.
- Well defined monodisperse macromolecules (compare polymers) & have a uniform molecularweight.
- Nanoscale objects with a surface & interior.
- The classical polymerization process which results in linear polymers is usually random in nature &produces molecules of different sizes, whereas size &molecular mass of dendrimerscan be specially controlled during synthesis.
- Large dendrimers can host small molecules/nano particles but don't have a cmc.

Table 2: Some properties of dendrimer.[27]

S. No.	Properties	Dendrimer
1	Structure and shape	Compact and spherical/globular
2	Size	Range of 1-100 nm
3	Architecture	Regular
4	Structural control	Very high
5	Synthesis	Stepwise growth
6	Crystallinity	Non crystalline, amorphous materials, low glass temperatures
7	Reactivity	High
8	Aqueous solubility	High
9	Nonpolar solubility	High
10	Viscosity	Nonlinear relationship with molecular weight
11	Ionic conductivity	High
12	Compressibility	Low

Synthesis of Dendrimers

Dendrimers are just in between molecular chemistry and polymer chemistry. They relate to the molecular chemistry world by virtue of their step-by-step controlled synthesis, and they relate to the polymer world because of their repetitive structure made of monomers. The three traditional macromolecular architectural classes (i.e., linear, cross-linked, and branched) are broadly recognized to generate rather polydisperse products of different molecular weights. In contrast, the synthesis of dendrimers offers the chance to generate monodisperse, structure-controlled macromolecular architectures similar to those observed in biological systems. Dendrimers are generally preparedusing either a divergent method or a convergent one. In the different methods, dendrimer grows outward 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, thenew periphery of the molecule is activated for reactions with more monomers.

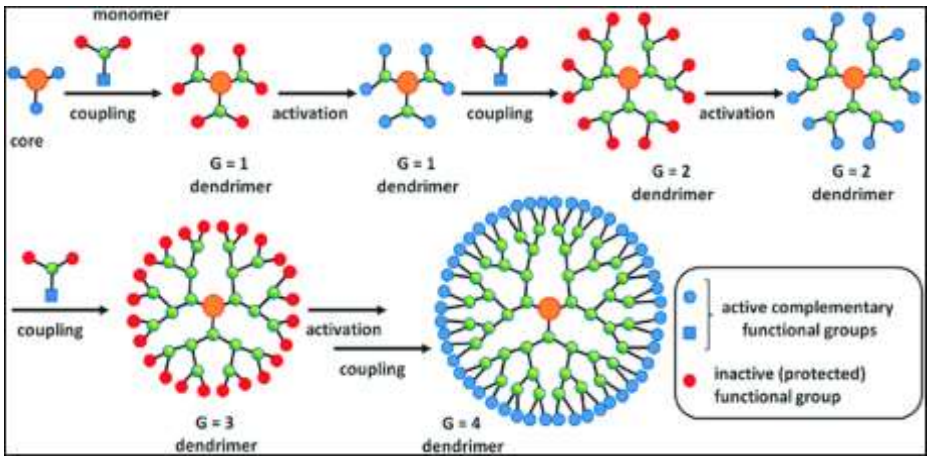

Figure 6: Synthesis of Dendrimers.[34]

Dendrimer for cancer treatment in clinical trials[32]

Dendrimers are increasingly being explored in clinical trials as innovative carriers for cancer treatment, offering the potential to enhance the efficacy and safety of chemotherapy. Various dendrimer formulations have been developed, each designed to target specific types of cancer with precision. For instance, the PAMAM dendrimer has been engineered as a dual-drug delivery system, combining cisplatin and small interfering RNA (siRNA) to target solid tumors more effectively. This dual approach allows for simultaneous disruption of cancer cell proliferation while silencing genes that promote tumor growth.

The following given dendrimer-based formulations in table 3 demonstrate the versatility and potential of dendrimers in cancer treatment, offering targeted, controlled, and efficient delivery of chemotherapeutic agents across a range of cancer types.

Table 3: Dendrimer for cancer treatment.

Sr.No.	Formulation	Type	Drug	Treatment/Uses
1	PAMAM # dendrimer	Dual-drug loaded dendrimer	Cisplatin and small interfering RNA #	Solid tumors
2	PAMAM-PEG # dendrimer	PEGylated dendrimer	Doxorubicin	Breast, bladder, ovarian, lung and thyroid cancer
3	Folic acid-PAMAM dendrimer	PPI #-dendrimer	Methotrexate	Epithelial cancer
4	PAMAM-PEG dendrimer	PEGylated dendrimer	5-Flouro uracil	Pancreatic cancer

Dendrimers Drug Delivery: Targeted and Controlled Release Drug Delivery

Due to its special qualities—namely, their well-defined three-dimensional structure, the availability of several functional surface groups, their low polydispersity, and their capacity for mimicking—dendrimers have drawn interest as potential drug carriers. Both the surface groups and the inside of the dendrimers can have drug molecules linked to them. Drugs can be carried by dendrimers in main two ways: either by being encapsulated inside the dendritic structure, or by interacting with drugs at their terminal functional groups through the formation of covalent or electrostatic interactions (prodrug).

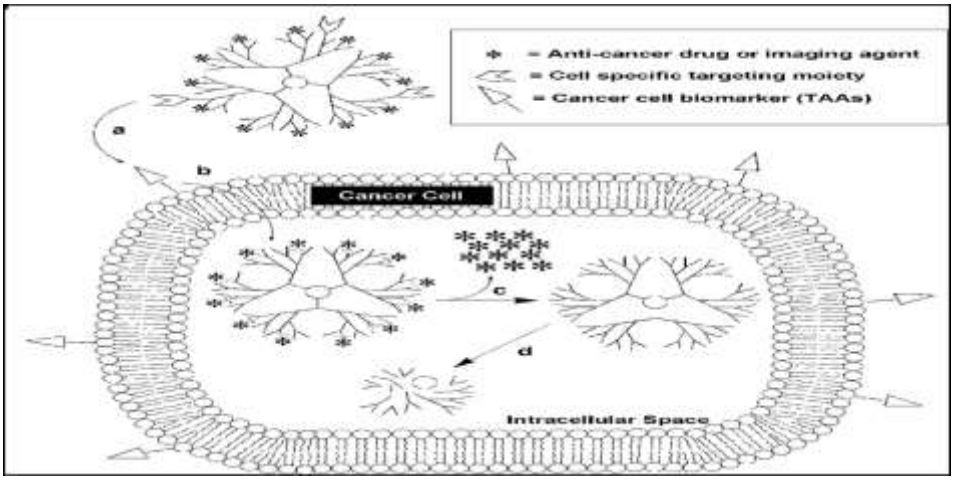

Figure 7: Cancer targeted drug delivery.[33]

Dendrimers for controlled release drug delivery: Adriamycin and methotrexate, two anticancer medications, were encapsulated inside G=3 and 4 PAMAM dendrimers that had been surface-modified with PEG monomethyl ether chains (i.e., 550 and 2000 Da, respectively). medication releases in vitro more slowly and sustainably than cellulose membrane control. Generation 4 (G4) PAMAM dendrimers with an amine termination could form a compound with flurbiprofen to provide controlled release.

Dendrimers in targeted drug delivery: Due of their excellent qualities, dendrimers are used in targeted drug delivery systems. Folic acid is one of the most efficient agents for cell-specific targeting that dendrimers can give. When compared to non-PEGylated dendrimers, PAMAM dendrimers treated with carboxymethyl PEG5000 surface chains had reasonable drug loading, a lower release rate, and a lower hemolytic toxicity. According to reports, the star polymer showed the most encouraging outcomes in terms of cytotoxicity and systemic circulatory half-life (72 hours).

Dendrimers in Gene Transfection (For Gene Delivery): Delivering pieces of DNA to specific parts of a cell involves challenges, during the delivery process primarily maintaining the integrity and activity of the DNA. Dendrimers, a class of synthetic polymers with a branched, tree-like structure, have shown promise in facilitating gene transfection due to their unique properties. PAMAM dendrimer-DNA complexes were used to encapsulate functional biodegradable polymer films for substrate mediated gene delivery.

For nanoparticles encapsulation: Dendrimers are also used in the synthesis of mono disperse metallic nanoparticles. PAMAM, dendrimers are utilized for their tertiary amine

groups at the branching points within the dendrimer. Metal ions are to an aqueous dendrimer solution and the metal ions form a complex with the lone pair of electrons present at the tertiary amines. After complexion, the ions are reduced to their zerovalent states to form a nanoparticle that is encapsulated within the dendrimer.[33]

CONCLUSION

The biomedical application of nanoparticles has seen remarkable advancements in recent years, driving significant progress in drug delivery systems and therapeutic interventions. However, despite this rapid growth, our current understanding of the long-term safety and biocompatibility of nanocarriers remains limited. This gap in knowledge underscores the need for comprehensive studies to fully evaluate the potential risks associated with nanotechnology in medicine.

Dendrimers, in particular, stand out due to the exceptional level of control they offer over their architectural features, including size, shape, branching length, and density, as well as surface functionality. This precise control over their structure enables dendrimers to be finely tuned for specific biomedical applications, enhancing their effectiveness as drug delivery vehicles. The unique structural attributes of dendrimers allow for the encapsulation and targeted delivery of therapeutic agents, improving the solubility, stability, and bioavailability of drugs while minimizing side effects.

As the field of nanomedicine continues to evolve, dendrimers are poised to play a pivotal role in the future of drug delivery and therapy. Their ability to meet the stringent demands of cost-benefit analysis, combined with their versatile and customizable nature, positions them as a promising tool in the development of advanced biomedical solutions. In conclusion, while further research is needed to fully understand the safety implications, dendrimers hold significant promise and are likely to be at the forefront of innovations in drug delivery and biomedicine.

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Nil.

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICTS OF INTERESTS

All authors have declared no conflict of interest.

REFERENCES

1. *What Is Cancer?* (2021, October 11). Cancer.gov. https://www.cancer.gov/about-cancer/understanding/what-is-cancer.
2. Kesharwani, P., Jain, K., & Jain, N. K. (2014). Dendrimer as nanocarrier for drug delivery. *Progress in Polymer Science*, *39*(2): 268–307. https://doi.org/10.1016/j.progpolymsci.2013.07.005.
3. Umapathy, V. R., Natarajan, P. M., & Swamikannu, B. (2023). Review of the Role of Nanotechnology in Overcoming the Challenges Faced in Oral Cancer Diagnosis and Treatment. *Molecules/Molecules Online/Molecules Annual*, *28*(14): 5395. https://doi.org/10.3390/molecules28145395.
4. Calixto, G., Fonseca-Santos, B., Chorilli, M., & Bernegossi, J. (2014). Nanotechnology-based drug delivery systems for treatment of oral cancer: a review. *International Journal of Nanomedicine*, 3719. https://doi.org/10.2147/ijn.s61670.
5. Tanaka, T., & Ishigamori, R. (2011). Understanding Carcinogenesis for Fighting Oral Cancer. *Journal of Oncology*, *2011*; 1–10. https://doi.org/10.1155/2011/603740.
6. Siegel, R. L., Miller, K. D., & Jemal, A. (2016). Cancer statistics, 2016. *CA: A Cancer Journal for Clinicians*, *66*(1): 7–30. https://doi.org/10.3322/caac.21332
7. Abbasi, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadi, H. T., Joo, S. W., Hanifehpour, Y., Nejati-Koshki, K., & Pashaei-Asl, R. (2014a). Dendrimers: synthesis, applications, and properties. *Nanoscale Research Letters*, *9*(1). https://doi.org/10.1186/1556-276x-9-247.
8. Abbasi, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadi, H. T., Joo, S. W., Hanifehpour, Y., Nejati-Koshki, K., & Pashaei-Asl, R. (2014b). Dendrimers: synthesis, applications, and properties. *Nanoscale Research Letters*, *9*(1). https://doi.org/10.1186/1556-276x-9-247.
9. Srinivasa-Gopalan S, Yarema KJ: *Nanotechnologies for the Life Sciences: Dendrimers in Cancer Treatment and Diagnosis, 7:* New York: Wiley; 2007.
10. Klajnert B, Bryszewska M: Dendrimers: properties and applications. *Acta Biochim Pol*, 2001; 48: 199–208.
11. Tomalia DA, Frechet JMJ: Discovery of dendrimers and dendritic polymers: a brief historical perspective. *J Polym Sci A Polym Chem*, 2002; 40: 2719–2728.

12. Zimmerman SC: Dendrimers in molecular recognition and self-assembly. *Curr Opin Colloid Interfac Sci*, 1997; 2: 89.
13. Zeng FW, Zimmerman SC: Dendrimers in supramolecular chemistry: from molecular recognition to self-assembly. *Chem Rev*, 1997; 97: 1681.
14. Moore JS: Shape-persistent molecular architectures of nanoscale dimension. *Acc Chem Res*, 1997; 30: 402.
15. Zimmerman SC, Lawless LJ: *Topics in Current Chemistry: Supramolecular Chemistry of Dendrimers, Volume 217*. New York: Springer, 2001.
16. Boris D, Rubinstein M: A self-consistent mean field model of a starburst dendrimers: dense core vs. dense shells. *Macromolecules*, 1996; 29: 7251–7260.
17. Tomalia DA, Baker H, Dewald JR, Hall M, Kallos G, Martin S: A new class of polymers: starburst-dendritic macromolecules. *Polym J*, 1985; 17(1): 117–132.
18. Spataro G, Malecaze F, Turrin CO, Soler V, Duhayon C, Elena PP: Designing dendrimers for ocular drug delivery. *Eur J Med Chem*, 2010; 45(1): 326–334.
19. Tomalia DA, Hedstrand DM, Ferritto MS: Comb-burst dendrimer topology: new macromolecular architecture derived from dendritic grafting. *Macromolecules*, 1991; 24: 1435.
20. Maciejewski M: Concepts of trapping topologically by shell molecules. *J Macromol Sci Chem*, 1982; A17: 689.
21. Kim YH, Webster OW: Water soluble hyperbranched polyphenylene: "a unimolecular micelle?". *J Am Chem Soc*, 1990; 112: 4592.
22. Newkome GRM, Baker GR, Saunders MJ, Grossman SH: Uni-molecular micelles. *Angew Chem Int Ed Engl*, 1991; 30: 1178.
23. Carvalho A., Fernandes A. R., Baptista P. V. *Applications of Targeted Nano Drugs and Delivery Systems*. Elsevier; 2019. Nanoparticles as delivery systems in cancer therapy, pp. 257–295.
24. Astruc D., Boisselier E., Ornelas C. Dendrimers designed for functions: from physical, photophysical, and supramolecular properties to applications in sensing, catalysis, molecular electronics, photonics, and nanomedicine. *Chemical Reviews*, 2010; 110(4): 1857–1959. doi: 10.1021/cr900327d.
25. McMahon M. T., Bulte J. W. M. Two decades of dendrimers as versatile MRI agents: a tale with and without metals. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, 2018; 10(3): e1496. doi: 10.1002/wnan.1496.
26. Madaan K., Kumar S., Poonia N., Lather V., Pandita D. Dendrimers in drug delivery and

targeting: Drug-dendrimer interactions and toxicity issues. *Journal of Pharmacy & Bioallied Sciences*, 2014; 6(3): 139–150. doi: 10.4103/0975-7406.130965.

27. Zahin N., Anwar R., Tewari D., et al. Nanoparticles and its biomedical applications in health and diseases: special focus on drug delivery. *Environmental Science and Pollution Research*, 2020; 27(16): 19151–19168. doi: 10.1007/s11356-019-05211-0.
28. Mittal, P., Saharan, A., Verma, R., Altalbawy, F. M. A., Alfaidi, M. A., Batiha, G. E. S., Akter, W., Gautam, R. K., Uddin, M. S., & Rahman, M. S. (2021). Dendrimers: A New Race of Pharmaceutical Nanocarriers. BioMed Research International, 2021; 1–11. https://doi.org/10.1155/2021/8844030.
29. Cai H., Dai X., Wang X., Tan P., Gu L., Luo Q., Zheng X., Li Z., Zhu H., Zhang H. A nanostrategy for efficient imaging-guided antitumor therapy through a stimuli-responsive branched polymeric prodrug. *Adv. Sci*, 2020; 7: 1903243. doi: 10.1002/advs.201903243.
30. Xu K., Wang M., Tang W., Ding Y., Hu A. Flash nanoprecipitation with Gd(III)-based metallosurfactants to fabricate polylactic acid nanoparticles as highly efficient contrast agents for magnetic resonance imaging. *Chem. Asian J.*, 2020; 15: 2475–2479. doi: 10.1002/asia.202000624.
31. Pérez-Herrero E., Fernández-Medarde A. Advanced targeted therapies in cancer: Drug nanocarriers, the future of chemotherapy. *Eur. J. Pharm. Biopharm*, 2015; 93: 52–79. doi: 10.1016/j.ejpb.2015.03.018.
32. Alam F., Naim M., Aziz M., Yadav N. Unique roles of nanotechnology in medicine and cancer-II. *Indian J. Cancer*, 2015; 52: 1. doi: 10.4103/0019-509X.175591.
33. Chaudhari, H., Popat, R. R., Adhao, V. S., & Shrikhande, V. N. (2016). Dendrimers: novel carriers for drug delivery. ResearchGate. https://www.researchgate.net/publication/340022189_Dendrimers_novel_carriers_for_drug_delivery.
34. Sowinska, M., & Urbanczyk-Lipkowska, Z. (2014). Advances in the chemistry of dendrimers. New Journal of Chemistry, 38(6): 2168. https://doi.org/10.1039/c3nj01239e.
35. Kaur, D., Jain, K., Mehra, N. K., Kesharwani, P., & Jain, N. K. (2016). A review on comparative study of PPI and PAMAM dendrimers. Journal of Nanoparticle Research, 18(6). https://doi.org/10.1007/s11051-016-3423-0.
36. Abbasi, E., Aval, S. F., Akbarzadeh, A., Milani, M., Nasrabadi, H. T., Joo, S. W., Hanifehpour, Y., Nejati-Koshki, K., & Pashaei-Asl, R. (2014). Dendrimers: synthesis, applications, and properties. Nanoscale Research Letters, 9(1). https://doi.org/10.1186/1556-276x-9-247.

37. File:Diagram showing where genes are in cells CRUK 380.svg - Wikimedia Commons. (n.d.).https://commons.wikimedia.org/w/index.php?title=File:Diagram_showing_where_genes_are_in_cells_CRUK_380.svg&oldid=845250838.
38. Massadeh, S., & Aamery, M. A. (2016). Nano-materials for Gene Therapy: An Efficient Way in Overcoming Challenges of Gene Delivery. Journal of Biosensors & Bioelectronics, 07(01). https://doi.org/10.4172/2155-6210.1000195.