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A REVIEW ON DENDRIMERS: SYNTHESIS, PROPERTIES AND APPLICATION IN MEDICINE

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Abstract:
Dendrimers are hyperbranched molecules [1]. They are highly branched, monodisperse macromolecules. Structural Advantages allow dendrimers to play an important role in the fields of nanotechnology, pharmaceutical and medicinal chemistry. As a result of their unique behavior dendrimers are suitable for a wide range of biomedical and industrial applications. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached that is conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. There are attempts to us dendrimers in the targeted delivery of drugs and other therapeutic use. Dendrimers have very low polydispersity and high functionality. The review aims to emphasize on construction, characterization, drug delivery and possible application of dendrimers in various areas of research, technology and treatment [5].
***Key words**: Dendrimer, convergent, divergent, drug delivery.*

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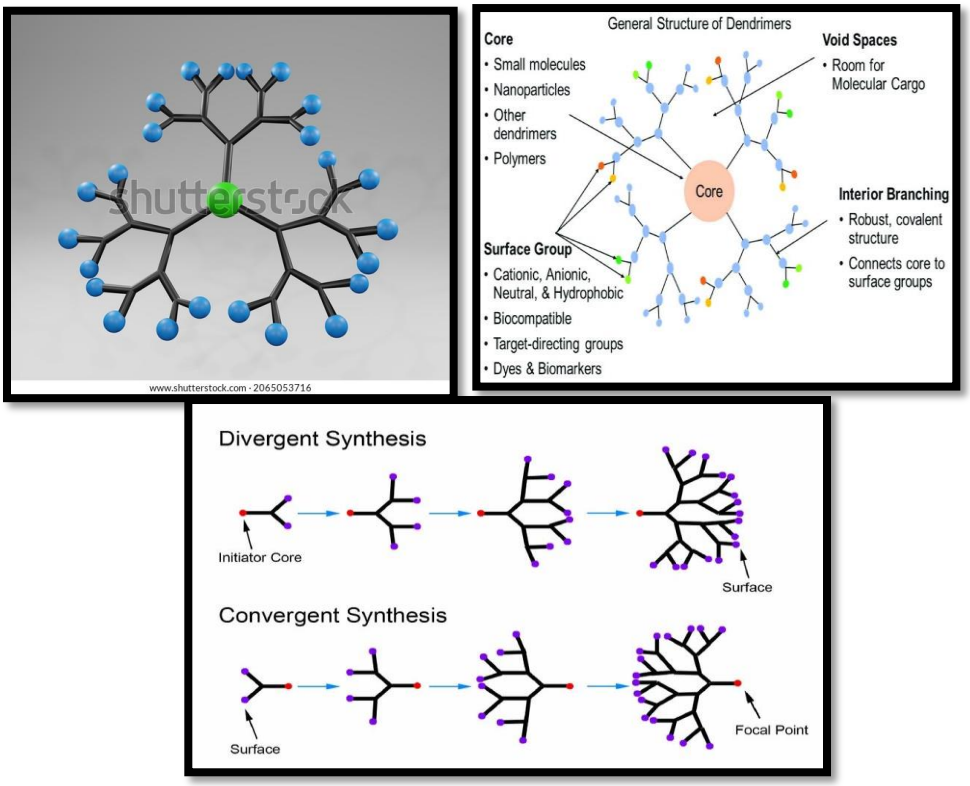
INTRODUCTION:

Dendrimers are hyperbranched molecules. A dendrimer is generally described as a macromolecule, which is characterized by its highly branched three dimensional structure that provides a high degree of surface functionality and versatility [2]. Dendrimers have often been referred to as the "Polymers of the 21st century". They were first discovered in the early 1980's by Donald Tomalia and co-workers. The term originates from 'Dendron' meaning a tree in Greek. The structure of Dendrimers tightly packed in the periphery and loosely packed in the core leaving spaces which play key role in the drug entrapping ability of Dendrimers [1].

The first synthesized dendrimers were polyamidoamines (PAMAM). At the same time Newkome group independently reported synthesis of similar macromolecules they called 'arborols' [3]. A Dendron usually contains a single chemically addressable group called the focal point (branching points)[3]. Dendrimers are repetitively branched molecules consists of a monomer unit attached core, where a, leading to a monodisperse, tree-like, star-shaped having diameters in the 2 to 10 nm range [3].

The structure of dendrimer molecules begins with a central atom or group of atoms labelled as the core. From this central structure, the branches of other atoms called 'dendrons' grow through a variety of chemical reactions [4]. There are attempts to us dendrimers in the targeted delivery of drugs and other therapeutic use. Dendrimers have very low polydispersity and high functionality. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy.

Dendrimer built from starting material is nitrogen atom. Then carbon and other element added by chemical reaction. Dendrimer is composed of an initial core, interior branching composed of repeating units, radially attached to the interior core and exterior attached to the outermost interior generations. The components of the dendrimer structure includes Pincer, Shell, Generation and End Group. The outer shell of dendrimers contains a varying number of pincers formed by the last focal point headed before the dendrimer surface. The dendrimer shell is the generation space (i.e the homo-structural spatial segment) between the focal points. Generation number is the number of focal points present in the dendrimer counting from the core towards the dendrimer surface[2].



TYPES OF DENDRIMERS:

Dendrimer Type	Method of Synthesis	Use	Example	Reference
PAMAM Dendrimer Poly(amidoamine) Dendrimer	Divergent	Material Science, Biomedicine Computer toners	DendritechTM	[3]
Pamamos Dendrimer Radially layered poly (amido amine organosilicon) Dendrimers	Convergent and Divergent	Nano-lithography, Electronics, Photonics, Chemical catalysis Precursor for honeycomb like network preparations.	SARSOX	
PPI Dendrimer Poly-Propylene Imines	Divergent	Material science and biology.	Asramol by DSM	
Tecto Dendrimer	Divergent	Diseased cell recognition, Diseased state drug delivery diagnosis,	Starburst®, Mercapto	
Chiral Dendrimer	Convergent	Biomedical applications, chiral hosts for enantiomeric resolutions	Chiral dendrimers derived from pentaerythritol.	
Hybrid Dendrimer	Divergent	Biomedicals, Molecular electronics, Nanophotonics,	Hybrid dendritic linear polymer	
Liquid Crystalline Dendrimer	Divergent	Science and Engineering.	Mesogen functionalized carbosilane dendrimers	
Amphiphil Dendrimer	Divergent	Structure-directing agent, Use as polar part,	Superfect, Hydraamphiphiles	
Micellar Dendrimer	Divergent	Biological and medical applications, Drug delivery, Imaging agent.	Beclomethazone dipropionate	
Multiple Antigen Peptide Dendrimer	Convergent	In vaccines and diagnostic research	Vivagel	
Frechet Type Dendrimer	Convergent	Drug carrier, Purifiers, Organic synthesis,	Dendron Azides	

CLASSIFICATION OF DENDRIMERS [5]:

On the basis of properties: 1. Hydrophilic Dendrimers
2. Biodegradable Dendrimers
3. Asymmetric Dendrimers
4. Amino Acid Based Dendrimers
5. Glycodendrimers

On the basis of structure: 1. Simple Dendrimers
2. Crystalline Dendrimers
3. Chiral Dendrimers
4. Micellar Dendrimers
5. Amphiphillic Dendrimers
6. Metallodendrimers
7. Tectodendrimers
8. Hybrid Dendrimers
9. Multilingual Dendrimers
10. Multiple Antigen Peptide Dendrimers

METHOD OF SYNTHESIS:

The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis [3].

1. Divergent Method 3. Double Exponential and Mixed Method

2. Convergent Method 4. Hypercores and Branched Monomers Growth

1) Divergent Method:

- Dendrimers starts from the central core and extends towards the surface i.e. diverging into space
- Two step process:
  - ✓ Activation of functional surface group
  - ✓ Addition of branching monomers units
- Divergent approach is successful for the production of large quantities of dendrimers.
- It causes some difficulties in the purification of the final product.[7]

2) Convergent Method:

- Dendrimers starting from the end groups and progressing inwards.
- When the growing wedges are enough large, attached to a suitable core to give a complete Dendrimer.
- The convergent methodology also suffers from the yields in the synthesis of large structures.[7]

3) Double Exponential & Mixed Growth:

- Double Exponential growth, similar to a rapid growth technique for linear polymers, involves an AB_2 monomer with orthogonal protecting groups for the A and B functionalities.
- This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material.
- These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again.[7]

4) Hypercores & Branched Monomers Technique:

- Frechet group continued their efforts on research of hypercore & branched monomers.
- This method involves the pre assembly of oligomeric species, which can then be linked together to give dendrimer.[7]

PROPERTIES OF DENDRIMERS:

1) **Monodispersity:** Dendrimer are monodisperse having same size. Dendrimer synthesis is specifically controlled which reduces size variation unlike linear molecule synthesis produces random structure and high size variation. Dendrimer synthesized from convergent method having high monodispersity than other method. Most of structural defect occur during formation of high generation dendrimer because of incomplete reaction, steric hindrance problem.[3]
2) **Solubility:** Functional group present on surface decide solubility of dendrimer. Hydrophilic group on surface is soluble in polar solvent like water. Hydrophobic group on surface soluble in non-aqueous solvent. Internal cavity carries hydrophobic drug and improves solubility. In a solubility test with tetrahydrofuran as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester.[3]
3) **Size and Shape:** Size of Dendrimer is in nanometre. Due to less particle size not only dendrimer easily cross the cell membrane but also clearance from body is reduced. Dendrimers show some significantly improved physical and chemical properties because of their molecular architecture, as compared to traditional linear polymers. Shape of dendrimer depend upon generation of dendrimer. Lower generation Open planer elliptical shape. Higher generation Compact spherical shape.[3]
4) **Rheological Property:** In solution linear chains exist as flexible coils, in contrast dendrimers form a tightly packed ball which influences its rheological properties. Dendrimer having less viscosity than linear polymer. As molecular mass increases intrinsic viscosity increases upto 4th generation dendrimer then decreases.
5) **Crystallinity:** Dendrimer are non-crystalline and amorphous materials.[7]
6) **Immunogenicity:** Dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) they become non-immunogenic or less immunogenic.[7]
7) **Cytotoxicity:** Cytotoxicity of dendrimer depend upon core of dendrimer but it also affected by functional group present on surface of dendrimer having amino (-NH2) group at surface shows cytotoxic property but this also depend upon generation of

dendrimer and concentration. Higher generation dendrimers being the most toxic.[7]

8) **Polyvalency:** It is useful as it provides for versatile functionalization; it is also extremely important to produce multiple interactions with biological receptor sites, for example, in the design of antiviral therapeutic agents.[4]

9) **Electrostatic interactions:** Molecular recognition events at dendrimer surfaces are distinguished by the large number of often identical end-groups presented by the dendritic host. When these groups are charged, the surface may have as a polyelectrolyte and is likely to electrostatically attract oppositely charged molecules. One example of electrostatic interactions between polyelectrolyte dendrimers and charged species include the aggregation of methylene blue on the dendrimer surface and the binding of EPR probes such as copper complexes and nitroxide cation radicals.[4]

10) **Pharmacokinetic properties:** Pharmacokinetic properties are one of the most significant aspects that need to be considered for the successful biomedical application of dendrimers, for instance, drug delivery, imaging, photodynamic therapy, and neutron capture therapy. The diversity of potential applications of dendrimers in medicine results in increasing interest in this area. For example, there are several modifications of dendrimers' peripheral groups which enable to obtain antibody-dendrimer, peptide-dendrimer conjugates or dendritic boxes that encapsulate guest molecules.[4]

APPLICATION OF DENDRIMERS:

1) Biomedical Study: Dendrimers are widely used in the biomedical field where they are used as analogs to proteins, enzymes, and viruses where they are primarily used to focus the target cells and conjugated to the host dendrimeric cells, for example, poly (amidoamine) dendrimer.[4]

2) Magnetic Resonance: Dendrimers are extensively used in magnetic resonance to improve the contrasts of the image. For example, metallic dendrimers are used to create the magnetic resonance imaging contrast agent.[5]

3) Biomimics: Dendrimers are also used to mimic the variety of biomolecules and create the microenvironment.[5]

4) Solubility Enhancement: Dendrimers help in improving the solubility profile of the poor and sparingly soluble drugs which results in increased bioavailability of drugs.[5]

5) Stability Enhancement: Dendritic formulation aids in the stability of the ingredients inside the core and provides dynamic internal cavities where neutral molecules and ions can be placed to prevent degradation.[5]

6) Targeted Delivery: Dendrimers also aid in site-specific targeted drug delivery via targeting ligands and conjugate to the dendrimer surface.[5]

7) Dummy and Carrier for Formulations: Dendrimer molecules have the ability to cross the cell membranes because of uniform size; due to this property, they help in various pharmacological activities.[5]

8) Nanoparticles: Poly(amidoamine) (PAMAM) dendrimers are used as a nanoparticle because it has a tertiary amine group at the branching point. Metal ions are introduced in the aqueous solution of dendrimers, and metal ions form a complex with the lone pair of electrons present at the tertiary amines.[5]

9) Nanodrugs: Various dendrimeric formulations were used as nanodrugs in various diseases such as polylysine (PPL) dendrimers with sulfonated naphthyl groups which were used as antivirus. PPL dendrimers with tertiary alkylammonium groups attached to the surface are antibacterial, and chitosan dendrimer hybrids are used as antibacterial agents.[5]

10) Anticancer drugs: Perhaps the most promising potential of dendrimers is in their possibility to perform controlled and specified drug delivery, which regards the topic of nanomedicine. One of the most fundamental problems that are set toward modern medicine is to improve pharmacokinetic properties of drugs for cancer. Drugs conjugated with polymers are characterized by lengthened half-life, higher stability, water solubility, decreased immunogenicity, and antigenicity. Unique pathophysiological traits of tumors such as extensive angiogenesis resulting in hypervascularization, the increased permeability of tumour vasculature, and limited lymphatic drainage enable passive targeting, and as a result, selective accumulation of macromolecules in tumour tissue. This phenomenon is known as ‘enhanced permeation and retention’ (EPR). The drug-dendrimer conjugates show high solubility,

reduced systemic toxicity, and selective accumulation in solid tumors. Different strategies have been proposed to enclose within the dendrimer structure drug molecules, genetic materials, targeting agents, and dyes either by encapsulation, complexation or conjugation.[4]

11) **Dendrimers as MRI contrast agents:** Dendrimer-based metal chelates act as magnetic resonance imaging contrast agents. Dendrimers are extremely appropriate and used as image contrast media because of their properties.[4]
12) **Dendritic sensors:** Dendrimers, although are single molecules, can contain high numbers of functional groups on their surface. This makes them striking for applications where the covalent connection or close proximity of a high number of species is important. A fourth-generation poly (propylene amine) dendrimer was investigated decorated with 32 dansyl units at the periphery. Since the dendrimer contains 30 aliphatic amine units in the interior, suitable metal ions are able to coordinate. It was observed that when a Co2+ ion is incorporated into the dendrimer, the strong fluorescence of all the dansyl units is quenched. Low concentrations of Co2+ ions (4.6 ×10−7 M) can be detected using a dendrimer concentration of 4.6 × 10−6 M.[4]

APPLICATIONS IN DRUG DELIVERY:

1) **Oral drug delivery:** Dendrimers with diameters in the range of 2.5 to 6 nm seemed to offer the ideal progression to smaller and smaller systems. Problem of flocculation and aggregation of the system in-vivo, oral uptakes of dendrimers are not better as accepted. Using polyoxyethylene glycol chains or ionic groups can reduce this problem, but oral uptake is then hindered by the hydrophilic nature of the surface dendrimers. Dendrimer-drug size, molecular weight, surface charge, incubation time and concentration of active molecule impart different characteristics for oral delivery of dendrimers.[2]

2) **Ocular drug delivery:** Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability. Topical application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. It is generally agreed that the intraocular Bioavailability of topically applied drugs is extremely poor. These results mainly due to drainage of the excess fluid via nasolacrimal duct and elimination of the solution by tear turnover. Several research advances have been made in ocular drug delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome some of these disadvantages. Ideal ocular drug-delivery systems should be non-irritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable.[2]

3) **CNS delivery:** Dendrimers, are regularly branched polymer molecules with branches growing from one or several centers. They can be formulated non-covalently with biological agents, such as DNA or conjugated with pro-drug or imaging agents and thus can be used as delivery vehicles for drug therapy or molecular imaging. To the best of our knowledge dendrimers have not been evaluated so far for CNS delivery except for few studies on intratumoral delivery of dendrimer conjugates with anti-cancer agents to treat glioma.[2]

4) **Dendrimer-based nanoparticles for lung delivery:** The ability of PAMAM dendrimers was investigated to augment plasmid DNA gene transfer in-vivo and evaluates the targeting of the lung by alternative routes of administration. They suggested that vascular administration seemed to achieve expression in the lung parenchyma, mainly within the alveoli, while endobronchial administration primarily targeted bronchial epithelium, indicating that each delivery route requires different vectors to achieve optimal trans-gene expression that each approach appears to target different cells within the lung.[2]
5) **Hydrogel for Ocular Drug Delivery:** Dendrimeric for mutations which are used in the hydrogels are cross-linked networks that increase the volume in the aqueous solution. By the addition of polyethylene glycol groups, they are widely used in cartilage tissue production and for sealing the ophthalmic injuries and targeted delivery.

6) **Transdermal Drug Delivery:** Dendrimers are found to enhance solubility and plasma circulation via transdermal formulation. PAMAM dendrimers make complexes with the nonsteroidal anti-inflammatory drugs and lead to enhanced permeation through the skin and act as permeation enhancers, for example, indomethacin.
7) **Gene delivery:** The primary promise that the combination of understanding molecular pathways of disease and the complete human genome sequence would yield safer and more efficient medicines and revolutionize the way we treat patients has not been fulfilled to date. However, there is little doubt that genetic therapies will make a significant contribution to our therapeutic armamentarium once some of the key challenges, such as specific and efficient delivery, have been solved. Current research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer/DNA complexes were encapsulated in a water soluble polymer and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection. Based on this method, PAMAM dendrimer/DNA complexes were used to en-capsulate functional biodegradable polymer films for substrate-mediated gene delivery.[4]

SUITABILITY OF DENDRIMERS FOR PARKINSON'S DISEASE

In the studies it was discussed that ASN is known to help in regulating the dopaminergic system as well as synaptic function. Although its exact physiological function is still unknown, it is apparent that this protein can modify its conformation which can lead to aggregation later on. Its connection to several neurological disorders such as Parkinson's disease is justified by its presence on Lewy bodies as aggregates [11]

or clumps. As briefly discussed earlier, the dendrimers in focus in these articles are PAMAM generation 4 or PAMAM G4 dendrimer, carbosilane dendrimer, and three separate generations of cationic pyridylphenylene dendrimers. Characterization tests were also identified to highlight any similarities between Thioflavin-T fluorescence, circular dichroism spectroscopy, and other microscopic techniques, particularly transmission electron microscopy (TEM). The utilization of TEM helped in understanding the morphology of the prepared dendrimer. Their activity and effectiveness against the fibrillation and capability to aggregate were tested against human ASN, rotenone-treated hippocampal mouse cell line, and ovine particular prion protein inclusion bodies (PrP IB) but these in vitro tests details will not be covered in full synthesis on this study.[11]

In the study regarding carbosilane dendrimers, a substantial difference between the dendrimers effect and rotenone was observed with regard to the mitochondrial membrane potential and the amount of reactive oxygen species (ROS) released. Rotenone is a commonly used pesticide that has the capability to inflict damage to the mitochondria complex I. Its lipophilic nature allows it to enter the BBB quickly. This finding is deemed essential in this review as it will help in linking the use of dendrimers as a potential antioxidant. As a matter of fact, its intervention in the PD-linked rotenone-damaged cells recorded an approximately 90% cell viability for the brain-dopamine rotenone cell 7 (BDBR7) and 83% for brain-dopamine rotenone cell 11 (BDBR11) whilst rotenone had only 63%. BDBR7 and BDBR11 are the two types of dendrimers used in the featured study. From these numbers, it can be deduced that rotenone-damaged cells have already produced a substantial amount of ROS in the brain which causes the mitochondria to fail due to imminent cell death by oxidation. To establish the relationship clearly, the higher the ROS present in the cells, the lower the cell viability will be. Furthermore, the more cells exposed to oxidation, the higher the chances of cell death.

DRUGS FORMULATED WITH DENDRIMERS

Sr. No.	Drug	Dendrimer Type	Pharmacology	Reference
1.	**Famotidine**	**G5 PPI**	**Anti-ulcer**	**[9]**
2.	**Indomethacin**	**G5 PPI**	**NSAIDs**	
3.	**Amphotericin B**	**G5 PPI**	**Antifungal**	
4.	**Rifampicin**	**Monosylated PPI**	**Antitubercular**	
5.	**Lamivudin**	**Monosylated PPI**	**Anti-HIV**	
6.	**Efavirenz**	**PPI**	**Anti-HIV**	
7.	**Furosemide**	**G4 PAMAM**	**Diuretic**	
8.	**Erythromycin**	**G4 PAMAM**	**Bactericidal Antibiotic**	
9.	**Zidovudine**	**G4 PPI**	**Anti-HIV**	
10.	**Ketoprofen**	**PAMAM**	**NSAIDs**	
11.	**5 Fluorouracil**	**G4 PAMAM**	**Anticancer**	**[9]**
12.	**Propanolol**	**Lauroyl-G4 PAMAM**	**Antihypertensive**	
13.	**Pilocarpine**	**G2 & G4 PAMAM**	**Antiglaucoma**	
14.	**Niclosamide**	**G0 to G3 PAMAM**	**Anthelmintic**	
15.	**Etoposide**	**PAMAM**	**Anticancer**	
16.	**10-hydroxycamtothecin**	**Carboxylated Poly(glycerol succinic acid)**	**Anticancer**	
17.	**Timolol Maleate**	**G3 PAMAM**	**Antiglaucoma**	
18.	**Doxorubicin**	**G4 PAMAM Polylysine**	**Anticancer**	

DENDRIMERS BASED PRODUCTS UNDER CLINICAL TRIALS

Sr. No.	Product	Type	Role	Status	**Reference**
1	**Vivagel® BV**	**Curative Agent**	**Prevention & treatment of recurrent bacterial vaginosis (BV)**	**Phase-3 Clinical Trials**	**[10]**
2	**DEP® Docetaxel**	**Targeted Delivery**	**Anticancer**	**Phase-2 Clinical Trials**	
3	**DEP® Cabazitaxel**	**Therapeutic Agent**	**Anticancer to treat prostate cancer**	**Marketed & under clinical development for other types of cancer like (bladder, ovarian, breast)**	
4	**DEP® Irinotecan**	**Targeted Drug Delivery**	**Anticancer**	**In phase ½ clinical trial**	
5	**Vivagel® STI (vagina microbicide)**	**Curative Agent**	**Prevention of genital herpes, HIV & other STI's**	**Underway**	
6	**Partnered DEP® AZD0466**	**Targeted Delivery Agent (Nanomedicine formulation of Astra Zeneca**	**Anticancer agent**	**Phase-1 Clinical Trial**	

FUTURE PROSPECTIVES:

Dendrimers are highly specified, globular, synthetic polymers that have many features which make them useful in biological systems. The high degree of control over the architecture of dendrimers, their size, appearance, length and intensity of branching and their surface flexibility render these compounds suitable carriers for bio-medical applications such as drug delivery, gene transfection, and imaging. They could be used in various fields, such as photodynamic therapy, biomedicine, gene delivery and siRNA, oligonucleotide conjugation, immunology, and scanning. Looking into the future, the use of biodegradable dendrimers displays significant drug potentialities delivery dendrimers, thus providing the benefit of being converted under physiological conditions into small-size materials that can be metabolized or excreted from the body. In this case, the dendrimers and their degradation products should be of low toxicity. Drug encapsulation in dendritic structures is a popular drug delivery technique that can help solve to solubility issue of hydrophobic drugs like camptothecins, which have low water solubility. As already stated, dendrimers are considered to be an ideal gene delivery vehicle which is biodegradable to prevent bioaccumulation and subsequent cytotoxicity. The effectiveness of gene therapy depends heavily on the advancement of effective and safe nucleic acids (NAs) vectors. Additionally, the development of modern biodegradable, biocompatible vectors is highly necessary to avoid both bioaccumulation and cytotoxicity and fast clinical translation. Moreover, dendrimers have proved very useful in the design of biosensors, imprinting scaffolds, and artificial receptors. Medical imaging is now one of the essential tools for early, reliable diagnosis and monitoring of health care management which is projected to contribute to improved outcomes.[28]

CONCLUSION:

It can be concluded that the approach of higher control over the architecture of dendrimers, their size, shape, branching length and density, and their surface functionally, makes these compounds ideal carriers in biomedical application such as drug delivery, gene delivery and imaging. Dendrimers are characterized by individual features that make them hopeful candidates for a lot of application. A rapid increase of the importance in the chemistry of dendrimers has been observed since the first dendrimer was prepared [2]. Dendrimers are the chemically distinguished entities with modifiable biological properties. Although they were studied for the past two decades, their synthesis requires multistep chemical reactions. Several studies concluded that dendrimers can be a breakthrough success for the treatment and diagnosis of cancer. They are widely engaged in the novel drug delivery systems as per the patient compliance. Their structural properties make them ideal to be used in the drug delivery in various routes[5].

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