DENDRIMERS AS NOVEL DRUG CARRIERS

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ABSTRACT

A new class of polymeric polymers is called dendrimers. A dendrimer normally has symmetrical structure around the core and frequently adopts a spherical three-dimensional layout, which offers a high level of surface usefulness and adaptability. Due to their distinct three-dimensional structure, dendrimers are innovative synthetic polymeric systems with superior physical and chemical properties. Dendrimers are an excellent choice for drug delivery by a variety of routes due to their structural characteristics, such as their form, size, structure, branching, functionality, and density. Particularly, dendrimers three-dimensional architecture allows for the incorporation of a wide range of biologically active substances to create biologically active conjugates. They offer surfaces for the attachment of pharmaceuticals and have the capacity to encapsulate or bind drugs using a variety of processes, including physical encapsulation, electrostatic contact and covalent conjugation. As a result, scientists and researchers are now paying close attention to it. Both bioactive molecules like DNA, heparin, and other polyanion as well as medication moieties are compatible with them. This review contains, history of dendrimer, types of dendrimer, synthesis, mode of action, properties and applications of dendrimers.

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

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1. INTRODUCTION:

The Greek words dendron, which mean "tree" or "branch," and meros, which imply "part," combine to form the word dendrimer. Dendrimers are also referred to as "arboroles" or "cascade polymers." A unique class of structurally regulated macromolecules known as dendrimers has a shape like a tree or a star, with a centrally located hollow area, internal outlets and terminal groups that enhance the surface. Dendrimers are well-defined in terms of their length, shape, molecular weight and monodispersity. Reactivity is determined by the chemical makeup of the core, the shells surrounding it, branching within it and surface functions. Through these residences, it has produced a pronged mono-dispersed polymer with a diameter of 5 to 50 nanometers and distinctive structural and topological features.

2. HISTORY:

Dendrimer oligonucleotides are experts in a brand-new field of polymer science that is frequently referred to as "polymers of the 21st century." The first dendrimer chemistry was introduced in 1978 by Fritz Vogtle and colleagues. He created the initial molecules of the cascade, which later came to be known as a dendrimer. The Meijer and Mulhaupt groups created polypropylene imine (PPI) dendrimers based on these initially tiny hyper branched molecules in the early 1990s[4,5]. The so-called polyamidoamine dendrimers, sometimes referred to as PAMAM dendrimers, are a new family of dendrimers described by Tomalia et al. in 1983. They are based on a mixture of amines and amides. Throughout the 1980's and 1990's, numerous research teams reported the existence of additional dendrimer designs and new dendrimer designs are still being created today.

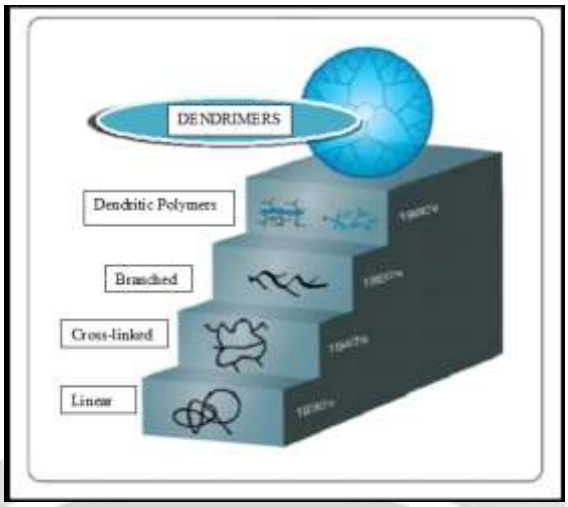


Fig.1: Development of Dendrimers

The synthesis of similar macromolecules was independently reported by Newkome and colleagues. They were known to as the arborols, which is derived from the Latin word arbour, which also means tree. Dendritic polymers are nanostructures that may be used for drug solubilization applications, DNA and oligonucleotide transport, drug targeting at specific receptor websites and ability to function as a facility for the construction of drug delivery device. Dendrimers are layer-by-layer (expressed in generations) synthesised core-shell nanostructures with a specific structure and low polydispersity that have a high level of controlling oversize, branching points and surfaceability. The greatest carriers for small molecule medications and biomolecules are dendrimers because of their ability to modify their characteristics to meet therapeutic needs.

Dendrimers have a wide range of unique properties due to their three-dimensional structure, including a nanoscaled globular shape, well-defined functional groups at the periphery, hydrophobic or hydrophilic cavities in the interior and extremely low polydispersity The drug can either be contained within the dendritic structure or interact with the terminal function groups via electrostatic or covalent bonding (prodrugs) depending on the drug-dendrimer system architecture. These dendrimers have emerged during the past ten years as promising nanocarriers for a range of medications. As a result, they have a variety of potential applications, including anti-inflammatory, antibacterial and anticancer medications, when administered via various routes.

3. STRUCTURE OF DENDRIMERS:

Dendrimers are typically ellipsoid or globular in shape, and they are made up of three different parts:

1) A centre core

2) Internal layers (generations), radially attached to the internal core, made up of repeating units.

2) Interior layers (generations) composed of repeating units, radically attached to the interior core.

Nano scale symmetrical molecules called dendrimers. A small atom or set of small atoms is encircled by symmetric branches called dendrons in dendrimers. The word dendron is also encountered frequently. A dendron usually contains a single chemically addressable group called the focal point or core. Although the terms are frequently used interchangeably, the figure below shows the distinction between dendrons and dendrimers.

Dendrimers consist of three basic components: the shell, pincer and end group. The dendrimer shell is the homo-structural spatial segment between the focal points, the "generation space". The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred to as the dendrimer interior. In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface.

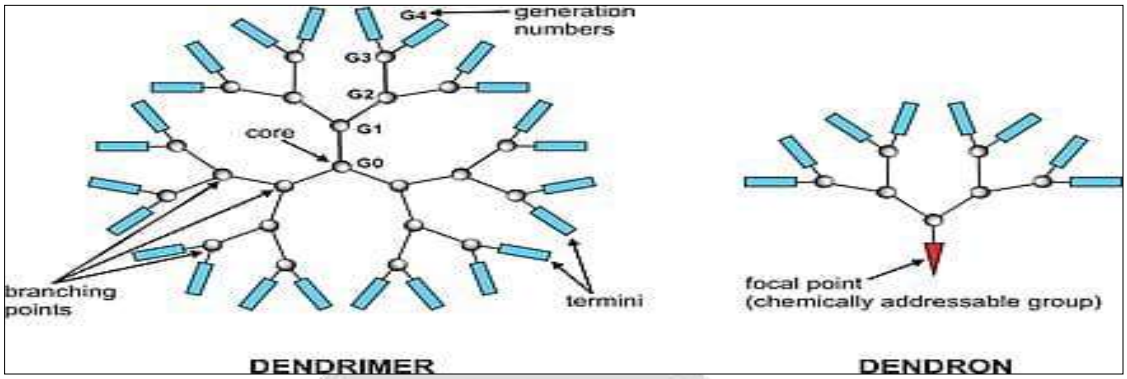


Fig.2: Representation of Dendrimer and Dendron.

In PPI and PAMAM dendrimers the number of pincers is half the number of surface groups (because in these dendrimers the chain divides into two chains in each focal point). End group is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "amino- terminated dendrimers".

At least two reactive functional groups should be present in the central core of the molecule. The recurring branches are arranged into "generations," which are a collection of wildly concentrically layers. Dendrimer generation is the hyperbranching that occurs as a dendrimer moves from its Centre outward. The focal points (branching points) produce homostructural layers between them. The generation is the total number of focal points along the path from the core to the dendrimer surface. On the surface of dendrimer molecules are the surface functional groups, which greatly influence the physical characteristics of dendrimers in solid state or in aqueous solutions. The number of surface functional groups as well as the molecular weight and size of dendrimers, are related with its generation and can be controlled during synthesis. The number of surface functional groups, as well as the molecular weight and size of dendrimers, are related with its generation and can be controlled during synthesis.

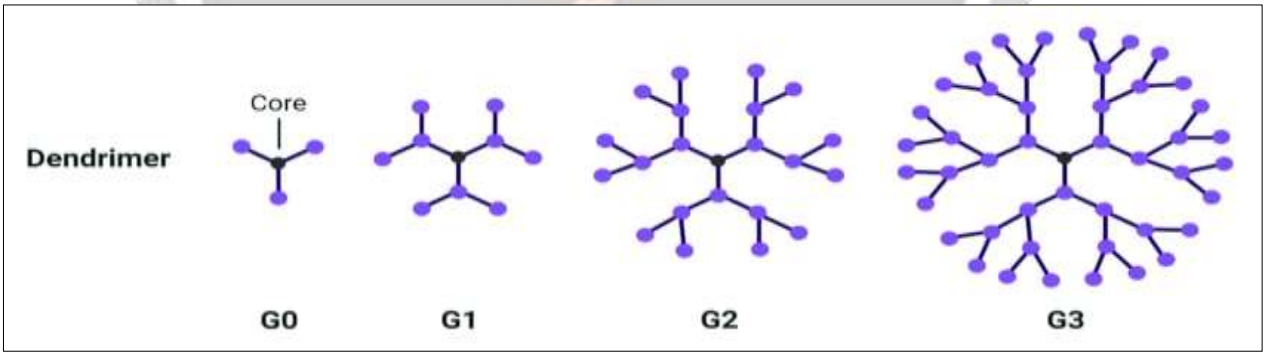
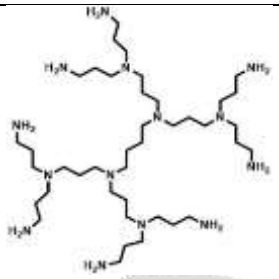
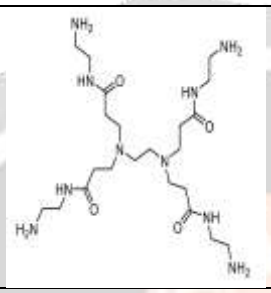
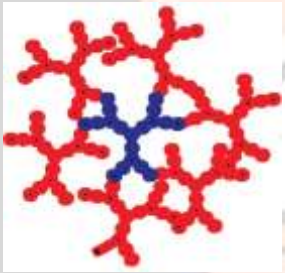
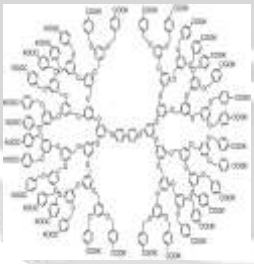
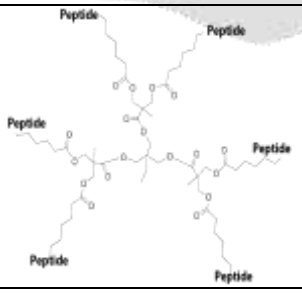
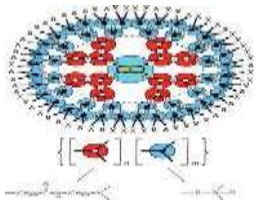
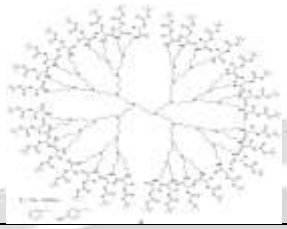
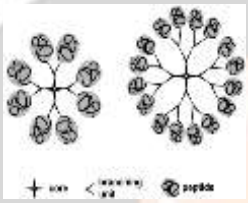
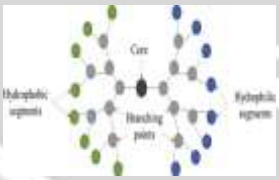


Fig.3: Structure of Dendrimer with Different Generations.

Table 1: Different type of Dendrimers.

Sr. No.	Types of Dendrimers	Structure	Synthesis	Identification and Example
1.	PPI(Poly Propylene Imine Dendrimer		Divergent	Its core structure is based on Diamino butane with primary amines as end groups and tertiary propylene amines as the center. These are generally available up to G-5 and are widely used in material science and biology. Example, Asramol by DSM (Netherlands)
2.	PolyAmido Amines (PAMAM)		Divergent	Spheroidal or ellipsoidal. It has great solubility and reactivity due to the rate of several functional end groups and empty internal cavities. Example, Dendritech TM (USA)
3.	Tecto Dendrimer		Divergent	These were made up of core dendrimers, which can be surrounded by other dendrimers, which effect a specific function leading to a smart therapeutic system used to diagnose the disease state and deliver API to the accepted disease cell. Example, StratusCS Acute Care TM, Starburst®, Mercapto.
4.	Frechet Type Dendrimers		Convergent	These were based on polybenzyl Ether hyper branched skeleton. The carboxylic acid group is attached to the surface of dendrimers that provides a site for further functionalization and also improve the solubility of dendrimers. Example, Frechet type dendronazides, TM Priostar.
5.	Multiple Antigen Peptide dendrimers		Convergent & Divergent	These are dendron-like molecular assembly based upon a polylysine frame. Lysine with its alkyl amino side-chain performed as an excellent monomer for the overture of frequent branching points. Example, vaccine and diagnostic Research

6.	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers		Convergent & Divergent	These are silicon-containing commercial dendrimers which are inverted unimolecular micelles and containexterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamine. Example, SARSOX
7.	Chiral Dendrimers		Convergent	The chirality of the dendrimers was based upon the structure of constitutionally different but chemically alike branches to thechiral core. For example, chiral dendrimers are derived from pentaerythritol.
8.	Peptide Dendrimers		Convergent	Peptide dendrimers are those, which hold amino acid as branching or interior units. These are used for diagnostic purposes and vaccine delivery. Example, Beta Casomorphin (human).
9.	Hybrid Dendrimers		Divergent	These dendrimers have characteristics of both dendritic and linear polymer. Example,Hybrid dendritic linear polymer, Polysilsesquioxanes.
10.	Amphiphilic Dendrimers		Divergent	These have one-half that is electron-donating and another half is electron retreating. Example, SuperFect, Hydraamphiphiles and bola-amphiphiles.

4. SYNTHESIS OF DENDRIMERS: For the synthesis of dendrimers, there are two main techniques:

4.1. Divergent Approach:

The divergent growth approach was the first to be proposed, and it remains the most used today. This technique is based on Tomalia and Newkome's pioneering work as well as Vögtle's branching model work. The creation of the dendrimer in the divergent process begins in the core and progresses to the periphery. To enhance the reaction with a new monomer, this approach involves two steps:

(i) Coupling of monomers and

(ii) Activation of the monomer end-group.

The divergent growth approach consists of repeating the two preceding processes until the necessary dendrimer production is

obtained. The initial generation of the dendrimer begins with the activation or alteration of the core and the coupling of the first monomer, resulting in divergent processing. The first generation (G1) is then activated in order to react with additional branched monomers and create the second generation (G2), and so on. When a new layer of branching units is generated, a new generation is created with the number of branched layers from the core corresponding to the generation number. To avoid deficiently created branches in the divergent method, it is critical that each phase of the reaction be fully finished before adding a new generation. In each stage of the synthesis, the surface of the dendrimer may be readily functionalized and changed, resulting in the desired pharmaceutical excipient at the end. Usually, the divergent approach leads to the synthesis of highly symmetric dendrimer molecules.

4.2. Convergent Approach:

Another way for constructing finely controlled dendritic topologies is the convergent approach. The branching architecture in the convergent method begins from the molecular surface of the dendron and proceeds to a reactive focus point, culminating in the production of a single reactive dendron. Its core operations, like the divergent method, include a coupling phase and an activation step. It allows for more structural control than the prior method. It features a modest number of simultaneous reactions at each development phase, resulting in a product with unrivalled purity and functional diversity. Because of the nanoscale steric problems encountered while connecting the dendrons to the molecular level core, the convergent technique is often confined to the synthesis of just lower generation dendrimers.

In the convergent method, a new dendrimer molecule is formed by starting the synthesis from the outside of the molecule and substituting the outermost branches, just as in the divergent method, which starts from the central moiety and has significant substitution branches attached to it. By counting the branches that are connected to the output molecule, this type of synthesis method can predetermine the fundamental structure of the final product molecule. The molecule is then activated at its new perimeter for a variety of interactions with monomers.

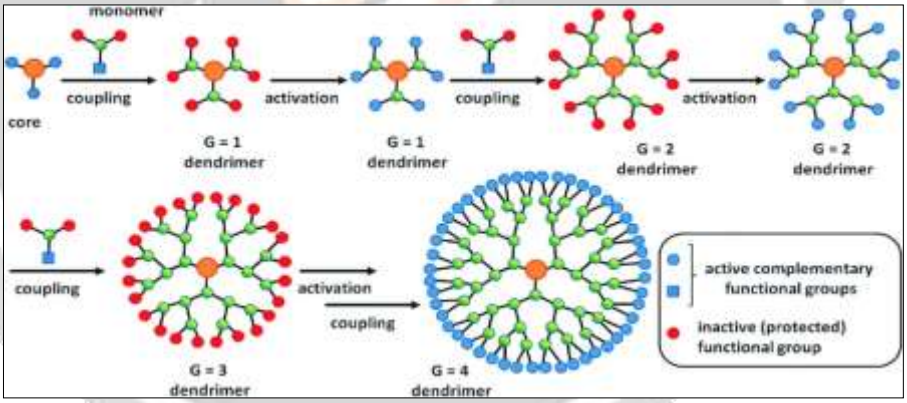


Fig.4: Synthesis of Dendrimer with Divergent Method

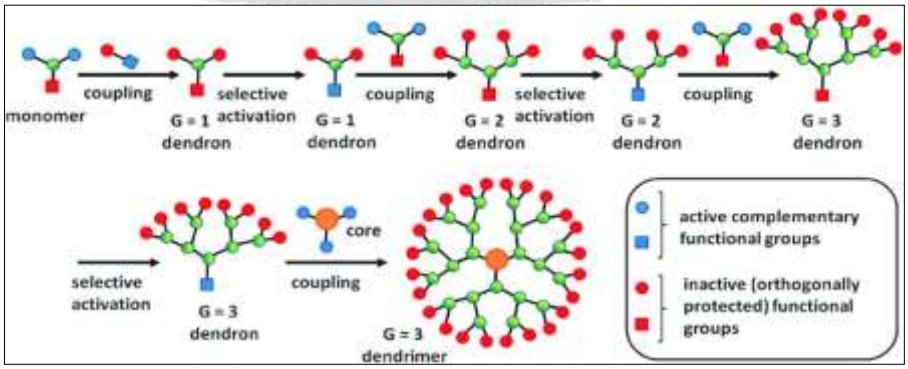


Fig.5: Synthesis of Dendrimer with Convergent Method

5. PROPERTIES OF DENDRIMERS:

1.Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymer.

2. Well defined monodisperse macromolecule (compare polymers) and have uniform molecular weight.

3.Nanoscale sizes which have similar dimensions to vital bio-building blocks as an example, proteins, DNA.

4.The solubility & reactivity of dendrimer is strongly influenced by the nature of surface groups.

5. Dendrimers terminated in hydrophilic groups are soluble in polar solvents.

6. Dendrimers having hydrophobic end groups are soluble in non-polar solvents.

7. Dendrimer solutions have significantly lower viscosity than linear polymers because entanglement or interpenetration of dendrimers is unfavorable due to their densely packed surface.

8. In large dendrimers, the surface is highly congested, where as a substantial amount of free space is encapsulated in the interior part, which allows for a wide range of applications such as site specific pockets for the accommodation of a variety of guest molecules.

9. Numbers of terminal surface groups appropriate for bio-conjugation of drugs, signaling corporations, concentrated on moieties or biocompatibility businesses.

10. Surfaces that can be designed with determined administrations to reinforce or face up to trans-mobile, epithelial or vascular bio-permeability.

11. An interior void space may be used to encapsulate small-molecule pills, metals or imaging moieties. Encapsulating in that void space reduces the drug toxicity and helps managed release.

12. Positive biocompatibility patterns, which are associated with lower phase anionic or neutral polar terminal surface groups, compared to higher generation impartial polar and cationic surface groups

13. Non- or low-immunogenicity associated with most dendrimer surfaces changed with small functional groups or polyethylene glycol (PEG).

14. Surface groups that may be changed to optimize bio-distribution; receptor-mediated focused on,

therapy dosage or controlled release of drug from the interior space.

6. BIOLOGICAL PROPERTIES:

1.Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications.

2.Size is a key determinant of dendrimer cytotoxicity for both PAMAM and PPI dendrimers.

3.Cytotoxicity of PAMAM dendrimers increases with generation for both full generation cationic dendrimers (G2-G4) and the "half-generation" anionic intermediates (G2.5, G3.5).

4.The nature and density of charged groups are other factors that determine dendrimer toxicity.

5.Cationic (surface) charges are in general more toxic but details depend on the specific groups involved, that is, for amines it has been proposed that primary amines are relatively more toxic than secondary or tertiary amines.

6.A concentration dependent tendency to cause haemolysis and changes in erythrocyte morphology has been linked to the

presence of -NH2 groups.

7.Anionic dendrimers, bearing a carboxylate surface, are not cytotoxic over a broad concentration range.

Table.2: Properties of Dendrimers

Sr. No.	Properties	Dendrimer
1.	Structure and shape	Compact and globular
2.	Size	Range of 1-100 nm.
3.	Structure control	Very high.
4.	Synthesis	Stepwise growth.
5.	Architecture	Regular
6.	Crystallinity	Non crystalline, Amorphous materials, low glass temperature.
7.	Viscosity	Non linear relationship with molecular weight.
8.	Polydispersity	Monodisperse.
9.	Reactivity	High.
10.	Aqueous solubility	High
11.	Non-polar solubility	High
12.	Ionic Conductivity	High
13.	Compressibility	Low

7. MODE OF DRUG ENCAPSULATION IN DENDRIMERS:

The phenomenon of the release of the drug depends on the type of dendrimer and core moiety used. The drug release pattern follows different mechanisms such as simple encapsulation, electrostatic encapsulation and covalent conjugation.

7.1. Simple Encapsulation:

The ellipsoidal or spheroidal shape, empty internal cavities, and open nature of the architecture of dendrimers make it possible to directly encapsulate guest molecules into the macromolecule interior. These empty internal cavities are hydrophobic in nature, which make it suitable to interact with poorly soluble drugs through hydrophobic interactions. Moreover, the nitrogen or oxygen atoms in the internal cavities can interact with the drug molecules by hydrogen bond formation. In view of these specific properties, the relationship between the internal cavities of dendrimers and drug molecules may involve these supramolecular interactions like physical encapsulation, hydrophobic interaction and hydrogen bonding.

7.2. Electrostatic Encapsulation:

The high density of functional groups like amine groups and carboxyl groups on the surface of dendrimers have potential applications in enhancing the solubility of hydrophobic drugs by electrostatic interaction. The G3 PAMAM dendrimer with an ammonia core is taken as an example. It has a much higher amino group density when compared with classical linear polymers. Non-steroidal anti- inflammatory drugs with carboxyl groups, including ibuprofen, ketoprofen, diflunisal, naproxen and indomethacin, have been widely been complexed with dendrimers by electrostatic interactions. Some anticancer and antibacterial drugs have also been reported to be incorporated by this kind of interaction. The common property of these drug molecules is that they are weakly acidic drugs with carboxyl groups in the molecules.

7.3. Covalent Conjugation:

The presence of large numbers of functional groups on the surface of dendrimers makes them suitable for the covalent conjugation of numerous drugs with relevant functional groups.

In this case, the drug is covalently bound to dendrimers and its release occurs via chemical or enzymatic cleavage of hydrolytically labile bonds. The encapsulation of drug molecules within hydrophobic cavities or absorption of drugs to the surface of dendrimers via electrostatic interactions preserves the chemical integrity and pharmacological properties of drug molecules while covalent attachment of drugs to the surface groups of dendrimers through chemical bonds affords better

control over drug release, facilitating the tissue targeting and controlled drug delivery.

8. MECHANISM OF DRUG DELIVERY THROUGH DENDRIMERS:

Over the past 30 years, great attention was given to developing sustained release drug delivery systems and the polymeric drug delivery systems are most focused among all the systems. Dendrimers or dendritic polymers have a well-defined nanosized structure which makes them appropriate for oral, parenteral, pulmonary and nasal drug delivery. Both hydrophilic and lipophilic drugs can be delivered by dendrimers. They had shown massive potential as a drug delivery carrier because they can cross the cell membrane by both transcellular and paracellular pathways. The number and ratio of dendrimer surface groups can be modified, and hence, the related parameters like biodistribution, receptor-mediated targeting and release rate from the dendrimers are also modifiable. Dendrimers were found to be utilized as drug delivery agents for the treatment of various diseases like HIV infection and herpes simplex virus infection, as anti-inflammatory agents, as antidotes and as anti-Alzheimer's, anticoagulants, and anticancer agents.

Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure or by interacting with drugs at their terminal functional groups via electrostatic or covalent bonds forming prodrug.

There are broadly two mechanisms for drug delivery:

1) First one is by in vivo degradation of drug dendrimer covalent bonding which depends on presence of suitable enzymes or an environment capable of cleaving the bonds.

2) The second one is by releasing the drug due to changes in physical environment such as pH, temperature. This approach is independent of the external factors and takes place in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor) .

9. DENDRITIC POLYMER CHARACTERISATION:

9.1. The following microscopy techniques are used to characterize the dendritic polymer:

Scanning Microscopy: It creates a picture by making contact touch Q at a few angstroms of a sensitive canilever arm with a sample. For instance, atomic force microscopy.

Transmission Microscopy: Using electrons or light, images are produced that are more intense than the original with a resolution ultimately constrained by the wavelength of the source.

9.2. Spectroscopy and spectrometry techniques for characterizing the dendritic polymer include the following:

a) Mass Spectroscopy: It is used to characterize tiny dendrimers with masses < 3000 Dalton using chemical ionisation or rapid atom bombardment. For dendrimers with the ability to create solid multi charged species, electrospray ionisation is utilised.

b) UV-VIS Spectroscopy (UV-VIS): Provides data for tracking the synthesis of dendrimers. The range of chromophoric devices has an impact on the absorption band's intensity.

c) Infrared Spectroscopy (IR): Provides data for routine assessment of the chemical alterations occurring on the surface of dendrimers.

d) X-ray Diffraction (XRD): The chemical composition, structure, length, and shape of Dendrimer can be precisely determined using statistics from X-ray diffraction (XRD).

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

f) Fluorescence: This technique offers records for an increasing number of high-sensitivity fluorescence measurements used to quantify flaws at various points throughout the synthesis of dendrimers.

9.3. The following electrical methods are used to characterize the dendritic polymer:

a) Electrochemistry: It reveals the possibility of the interaction of electro active end groups.

b) Electron paramagnetic resonance (EPR): Quantitative assessment of the efficiency of substitution at the PANAM dendrimer floor.

c) Electrophoresis: It provides statistics regarding the evaluation of the homogeneity and purity of various types of water-soluble dendrimers.

9.4.Scattering Strategies Scattering Techniques For Characterization of The Dendritic Polymer Are As Follows

a) Small-angle x-ray scattering (SAXS): Offers information regarding their average radius of gyration (Rg) as a response. Statistics on the association of polymer segments are also provided by the scattering's depth.

b) Small-angle neutron scattering (SANS): Offers access to the gyroscope's radius, but it may also provide more accurate information than SAXS. Through SANS experiments using PAMAM and PPI dendrimers, the location of the finishing services has also been determined.

9.5. Physicochemical characteristics and rheology: The following physical properties and rheology were utilized to characterise the dendritic polymer:

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

b) IntrinsicViscosity: It is an analytical probe of the morphological shape of dendrimers.

9.6. Miscellaneous other techniques used of characterization of the dendritic polymer are as follows:

a) Sedimentation Technique: used for lactosylated PAMAM dendrimers, measurements of dipole moments for PMMH dendrimer.

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

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

10. ROLE OF DENDRIMER IN DRUG DELIVERY SYSTEM:

The dendrimers role in drug delivery is the utmost part of any dosage form to achieve its biopharmaceutical and pharmacological activity and benefits. Dendrimers act in two manners for drug delivery as in the formulation and nanoconstruct . Drugs are entrapped using noncovalent interactions whereas in nanoconstruct, dendrimers are covalently bonded. The phenomenon was explained using the use of PAMAM dendrimers . The structure having cavities along with an abundant terminal group results in spherical and defined branching of polymers resulting in the formation of stable complexes with drugs such as plasmid DNA, oligo-nucleotides, and antibodies. As reported, amine-terminated PAMAM dendrimers can solubilize different hydrophobic groups belonging to different families because the cationic charge present on the surface of the molecules disturbs the functionality of the cell membrane]. These modification changes lead to changes such as becoming more sensitive, effective increase of transdermal permeation, and specific drug targeting. Some examples of surface modifications are using PEGylation, acetylation, glycosylation, and amino acid functionalization leading to changes in the peripheral amine groups by neutralization which helps to improve dendrimer biocompatibility. Dendritic platforms can also be used to create nanodevices by altering and modifying the binding of ligands and imaging molecules. Dendrimer

nanotechnology is in the current line issue due to its multifunctional ability to produce next-generation devices.

11. APPLICATION:

As stated earlier, dendrimers are the branched tree-shaped repeating units of molecules containing a therapeutic entity inside the cavity. This property of dendrimers can be exploited to treat severe diseases like cancer. The different polymers have different branching capacities depending on their molecular weight and structure, and then accordingly, they have different drug payload capacities. The functional moieties present on their surface can be utilized to bind specific targeting moieties thereby achieving active targeting by the use of dendrimers.

11.1. Receent Progress of Dendrimers in Drug Delivery for Cancer Therapy:

With the recent advances of nanotechnology, dendrimers are emerging as a highly attractive class of drug delivery vectors for cancer therapy. Dendrimers are multifunctional smart nanocarriers to deliver one or more therapeutic agent, safely and selectively to cancer cells.

a) Drug delivery as carriers:

Dendrimers act as a carrier for the delivery of anti-cancer drugs by either encapsulation of the drug in the interior of the dendrimer or conjugating covalently to form macromolecular prodrug

b) Dendrimers with drug-encapsulation:

We looked into using poly (glycerol-succinic acid) dendrimers as camptothecin delivery systems. The Grinstaff group used G4-PGLSA dendrimers with hydroxyl and carboxyl peripheral groups to encapsulate 10-hydroxy camptothecin for delivery to cancer cells in a preliminary study. Methotrexate and 6-mercaptopurine were solubilized with melamine-based dendrimers, which also served to lessen toxicity.

The lack of controlled drug release kinetics in most of these delivery systems, which typically release their payload over the course of several hours, is a significant disadvantage. For this reason, direct intratumoral injection may be the most effective way to use drug-encapsulated dendrimer systems.

c) Dendrimer drug conjugates:

Anti-neoplastic agent is covalently attached to the peripheral groups of the dendrimer in a dendrimer drug conjugate. This approach has clear advantages over drug-encapsulated systems, such as the ability to attach multiple drug molecules to each dendrimer molecule.The release of therapeutic molecules is controlled by the nature of linkages.

To compare the anti-cancer activity of the drug delivered by a linear or dendritic carrier, paclitaxel was conjugated to PEG or G4PAMAM. When exposed to human ovarian carcinoma A2780 cells, both PEG and PAMAM significantly increased the aqueous solubility of paclitaxel (0.3mcg/ml) to 2.44mcg/ml and 3.2 mcg/ml respectively.

11.2. Dendrimer as Solubility Promoters:

There are many substances with potent therapeutic activity that have not been used for therapeutic purposes because they are not soluble in pharmaceutically acceptable solvents. Dendrimers that are water soluble can bind and dissolve small, acidic, hydrophobic molecules that have antifungal or antibacterial properties. In other words, they encapsulate poorly soluble drugs within the dendritic structure to make them more soluble. Surface ionic interaction was discovered to be the primary influence on PAMAM dendrimer solubilization behaviour, as opposed to interior encapsulation. PAMAM dendrimers of different generations (G2-G4) have the potential to significantly improve drug solubility. A higher drug bioavailability could be a result of the higher solubility.

11.3. Dendrimers in Oral Drug Delivery:

Drugs taken orally may have poor intestinal membrane penetration and low solubility in aqueous solutions.The various systems used to load drugs into oral drug carriers are the focus of current strategies to address these problems.The properties

of these macromolecular carriers played a major role in the absorption and distribution of drugs in such systems, so it is possible to reduce side effects by altering the structure of the macromolecules. Drugs administered orally should be able to resist deterioration in an ideal macromolecular carrier. Intestinal epithelium absorption may be improved and nonspecific interactions with food proteins may be reduced. By conjugating/encapsulating drug molecules to/into dendrimers with specific properties, they may serve as potential candidates for orally controlled release systems. They make it possible to maintain drug concentrations within the therapeutic range at the injured areas, which can make dosing regimens simpler. Dendrimers can also significantly improve the solubility of these orally administered medications and even the stability of medications in biological settings. The bioadhesive properties of these macromolecules have a strong affinity for mucosa and can extend the time that an orally administered drug is in contact with the intestinal epithelium. Furthermore, because dendrimers themselves have easy intestinal membrane penetration, they can improve the oral absorption of medicines with low penetration. As a result of these characteristics, dendrimers are suitable carriers for the creation of oral drug delivery systems.

11.4.Dendrimer as contrast agents in magnetic resonance imaging:

Metal chelates based on dendrimers excel as contrastants in magnetic resonance imaging. Due to their extensive properties, dendrimers are ideally suited and frequently used as image-differentiating media. Dendrimers have been the subject of numerous tests, and it has been revealed that they are a more potent contrast agent than conservational ones. Furthermore, the sixth generation polygadolinium dendrimer demonstrated a sustained improvement with a half-life of 200 min as opposed to 24 min for monovalent gadolinium agent. For 3D time-of-flight MR angiography, this extended augmented time is very helpful.

11.5. Dendrimer in ocular drug delivery:

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

11.6. Dendrimers in pulmonary drug delivery

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

11.7. Dendrimer in transdermal drug delivery:

Because dendrimers are distinctly water-soluble and biocompatible, they can successfully deliver drugs via transdermal formulations while improving their solubility and plasma circulation time. For instance, increasing the bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application and improving the drug permeation through the skin with NSAIDs like Ketoprofen and Diflunisal.

11.8. Dendrimers for boron neutron capture BNCT is commonly used approach to cancer treatment:

A non-radioactive medication is injected into the patient and it migrates specifically to cancer cells (those that contain a stable isotope of boron, B 10). The patient is then exposed to a neutral beam of thermal neutrons with low energy. Normal cells are unaffected as a result of the neutrons reaction with the boron in the tumour. The local concentration of B10 in the tumour should be 109 atoms per cell in order to achieve the desired effects of BNCT. Because of their multivalency and clearly defined structure, dendrimers are used as boron carriers. Example: PAMAM dendrimers that contain boron.

11.9. Dendrimers as nano-drugs:

HIV and other sexually transmitted diseases (STDs) may be prevented or reduced by the use of dendrimers as nano-drugs, which are effective as antiviral capsules against the herpes simplex virus. Poly(lysine) dendrimers have had their sulfonated naphthyl groups replaced. When PPI dendrimers with tertiary alkylammonium groups are attached to the surface, they demonstrate amazing antibacterial biocides against Gram-positive and Gram-negative bacteria. Chitosan-dendrimer hybrids have also been found to be useful as antibacterial agents, carriers in drug delivery systems and in different biomedical programmes.

TOXICITY AND PEGYLATION:

It is well known that dendrimers may be toxic, with the majority of this toxicity being attributed to the cationic dendrimers surface interactions with membranes that have a negative biological load and damage cellular membranes, leading to cytotoxicity and hemolytic toxicity. PAMAM dendrimers are therefore more cytotoxic when cationic than when anionic. The cationic dendrimer-G7 PAMAM, for instance, interacts with the lipid bilayers of cells by forming holes 15–40 nm in diameter, which disrupt the electrolyte's flow and result in cell death. With hydrophilic molecules and poly (ethylene glycol), which masks the surface charge of cationic dendrimers and improves biocompatibility and increases the solubility of the polymers, many toxic effects of dendrimers are attenuated at their surfaces. Compared to non-pegylated dendrimers, pegylated dendrimers have lower cytotoxicity and a longer blood half-life. As PEGylation rises. PEGylation increases the physical dendrimers size which reduces renal clearance.

12. DENDRIMER BASED PRODUCTS:

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

1. Alert ticket for Anthrax Detection

2. Priofect™, Priostar™, and Starburst for targeted diagnostic, therapeutic delivery for cancer cells.

3. SuperFect for Gene Transfection

4. Stratus CS for Cardiac Marker

5. Vivagel for preventing HIV

CONCLUSION

Dendrimer drug delivery systems are getting huge interest as an advantageous solution for delivering bioactive like drugs and gene. The structure of dendrimers posses greatest impact on their physical and chemical properties.The nanoscopic size and recognition abilities make dendrimers as ideal building blocks for self-assembly and self-organization systems. The cavities inside the dendritic structure can be modified to incorporate hydrophobic and hydrophilic drugs. The terminal groups are modified to attach antibodies and bioactive substances for targeting purpose along with providing miscibility, reactivity and solubility. Currently, dendrimers are of great interest for delivering drug molecules via different routes as a nanocarrier. Toxicity problems associated with cationic dendrimers are overcome by PEGylation which neutralizes the charge on them. Dendrimers possess suitable properties to establish itself as a potential carrier for delivery of therapeutic agents irrespective of certain synthetic and regulatory constraints. This review contains various structural aspects and properties of dendrimers along with their pharmaceutical application as a potential novel drug delivery carrier.

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