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Review Article

DENDRIMERS: A NEW GENERATION CARRIER

Anisha Agrawal, Sunisha Kulkarni

School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior (M.P.), India.

***Corresponding Author: Email** anisha.agrawal374@gmail.com

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ABSTRACT

Dendrimers are a novel class of synthetic macromolecules having highly branched, three dimensional, nanoscale structures with very low polydispersity and high functionality. The structure of these materials has a great impact on their physical and chemical properties. These unique features have made their application in nanotechnology, pharmaceutical and medical chemistry particularly attractive. As a result of their unique behavior, dendrimers are suitable for a wide range of biomedical and industrial applications. These carriers have well defined size, shape, molecular weight and monodispersity, which make the dendrimers a suitable carrier in drug delivery application. Dendrimers are unimolecular micelle in nature and due to this enhances the solubility of poorly soluble drugs. These polymers have also successfully proved themselves as useful additives in different routes of drug administration because they can render drugs of greater water solubility, bioavailability and biocompatibility. Dendrimers possess empty internal cavities and open conformations, which make it possible to encapsulate hydrophobic drug molecules. In addition, they have a much higher surface functional group density when compared with conventional macromolecules. This review article focuses on the various aspects of dendrimers including structure, properties, types of dendrimers, preparation methods and their applications in pharmaceutical as well as non-pharmaceutical field.

Keywords: Bioavailability, divergent, convergent, PAMAM, PAMAMOS.

INTRODUCTION

Dendrimers, a new class of polymeric materials are nano-sized, radially symmetrical with well-defined homogenous and monodisperse structure consisting of tree-like atoms or branches. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behavior, dendrimers are suitable for a wide range of biomedical and industrial applications. These are versatile, well-defined, compartmentalized polymers with sizes and physicochemical properties resembling to those of biomolecules like proteins. A macromolecular drug-delivery system is a complex material in which a drug is attached to a carrier molecule such as a synthetic polymer, antibody, hormone or liposome [1].

These hyper branched molecules were first discovered by Fritz Vogtle in 1978, Donald Tomalia and co-workers in the early 1980s, and at the same time, but independently by George R. Newkome. The word "dendrimer" originated from two words, the Greek word "dendron" meaning tree, and "meros" meaning part or unit. These might also be called as 'cascade molecules', but this term is not as much established as 'dendrimers'. Dendrimers are nearly monodisperse macromolecules that contain symmetric branching units built around a small molecule or a linear polymer core. Polyionic dendrimers do not have a persistent shape and may undergo changes in size, shape, and flexibility as a function of increasing generations [2].

Dendrimers have successfully proved themselves as useful additives in different routes of drug administration because they can render drugs of greater water solubility, bioavailability and biocompatibility. These carriers have well-defined molecular weights and host–guest entrapment properties. Since dendrimers are synthesized from branched monomer units in a stepwise manner, it is possible to conduct

a precise control on molecule size, shape, dimension, density, polarity, flexibility and solubility by choosing different branching units and surface functional groups. Dendrimers possess empty internal cavities and open conformations (for low-generation dendrimers), which make it possible to encapsulate hydrophobic drug molecules. In addition, they have a much higher surface functional group density when compared with conventional macromolecules. These functional groups permit the application of dendrimers to enhance the solubility of many drugs. Furthermore, the large number of surface functional groups on the outer shell is responsible for high reactivity, and thus dendrimers can be modified or conjugated with a series of interesting guest molecules. Drugs or other guest molecules can either be conjugated with these surface functional groups or encapsulated in the hydrophobic cavities of dendrimers. Such specific properties of the dendrimers make them most suitable for drug delivery systems [3].

Structure of Dendrimers

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added and the sphere can be expanded to the desired size by the investigator. The final entity is spherical macromolecular structure whose size is similar to blood albumin and hemoglobin [1].

A typical dendrimer structure consists of three components, namely [4] [5]:-

- An initiator core determines the size and shape of the dendrimer;
- Interior layers or generations composed of repeating units, radially attached to the interior core, determines the amount of void space that can be enclosed by the dendrimer; and
- Exterior layer attached to the outermost interior generations, allows growth of the dendrimer or other chemical modifications.

Dendrimer generation is hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal (branching) points. The number of focal points when going from the core towards the dendrimer surface is the generation number, i.e. a dendrimer having four focal points when going from the centre to the periphery is denoted as the 4th generation dendrimer. Here, this term is abbreviated to simply a G4-dendrimer, e.g. a 4th generation polypropylene imine is abbreviated to a "G4-PPI-" dendrimer. The core part of the dendrimer is sometimes denoted generation "zero", or in the terminology presented as "G0". The core structure thus presents no focal points, as hydrogen substituents are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted half-generations [6].

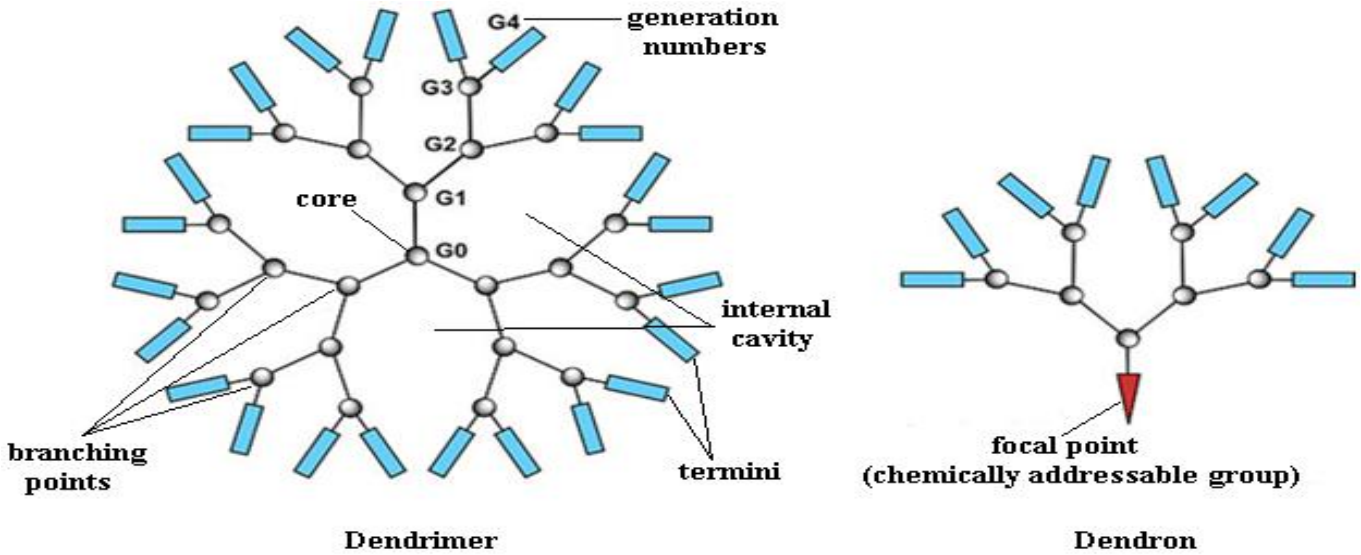

Figure 1: Representation of a fourth generation dendrimers [4] **–** It consists of a series of repetitive generating shells, starting with a central initiator core. Each subsequent shell represents a new "generation" of polymer with a larger molecular diameter, twice the number of reactive surface sites, and approximately double the molecular weight of the preceding generation.

The interior is thus well-suited for encapsulation of guest molecules. The three parts of the dendrimer can be tailored specifically for the desired purposes, e.g., dendritic sensors, vehicles or drugs. The multivalent surfaces on a higher-generation dendrimer can contain a very high number of functional groups. This makes the dendritic surfaces and outer shell well-suited to host- guest interactions where the close proximity of a large number of species is important.

Ideal Properties of Dendrimers

In order to apply dendrimers as tools for drug delivery devices in vivo, they have to fulfill several biological demands of crucial importance. The minimization of side effects of the drug can be altered by modifying the properties of the carrier. The ideal dendrimers should be [7]

I. Inert and non-toxic;
II. Biodegradable;
III. Non-immunogenic;
IV. Able to cross barriers such as intestine, blood-tissue barriers, cell membranes etc;
V. Able to stay in circulation for the time needed to have a clinical effect;
VI. Able to target to specific structures;
VII. Compatible with guest molecules;
VIII. Must protect the drug until it reaches to the desired site of action and release the drug.

Physicochemical Properties of Dendrimers

Many of the properties of dendrimers make them suitable for pharmaceutical applications which are as follows [1]:-

Nanoscale sized that have similar dimensions to important bio-building blocks, such as proteins, DNA etc.

It improves the pharmacokinetic and pharmacodynamics properties of a drug so that there is also an increase in bioavailability.

Multiple numbers of terminal surface groups (Z) suitable for bio-conjugation of drugs, signaling groups, targeting moieties or biocompatibility groups.

Surfaces may be designed with functional groups to augment or resist transcellular, epithelial or vascular biopermeability.

Interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties. Encapsulating in that void space reduces the drug toxicity and facilitates controlled release.

Positive biocompatibility patterns that are associated with lower generation anionic or neutral polar terminal surface groups as compared to higher generation neutral apolar and cationic surface groups.

None or low immunogenicity associated with most dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG).

Surface groups that can be modified to optimize bio-distribution; receptor mediated targeting, therapy dosage or controlled release of drug from the interior space.

Have ability to be excreted from body as a function of nanoscale diameter.

Size and molecular mass of dendrimers can be specifically controlled during synthesis which cannot be done for linear polymers.

These carriers have significantly lower viscosity than linear polymers. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline. Such behavior is unlike that of linear polymers.

These have high solubility, miscibility and reactivity due to the presence of many chain ends.

These carriers possess solubility in a large number of solvents. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents.

These carriers have the possibility to encapsulate guest molecules in the macromolecule interior.

Controlled and targeted release of drug can be achieved at sites restricted for drugs.

Distinct from traditional linear polymers, dendrimers synthesized step-by-step have well organized structures with a very low polydispersity.

It has the useful property of polyvalency as it provides for versatile funtionalization; it is also extremely important to produce multiple interactions with biological receptor sites, for example such as antiviral therapeutic agents.

Types of Dendrimers [8]

PAMAM Dendrimer – PAMAM or Poly (Amido Amine) dendrimers are spheroidal or ellipsoidal in shape. These are synthesized by the divergent method using ammonia or ethylenediamine as a starting material. The high solubility

and reactivity of these are due to presence of a number of functional end groups and empty internal cavities. PAMAM dendrimers are commercially available, usually as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a trisaminoethylene-imine core. The name refers to the star like pattern observed when looking at the structure of the high generation dendrimers of this type in two-dimensions

PAMAMOS Dendrimer – PAMAMOS or Poly (Amido Amine Organosilicon) are silicon containing first commercial dendrimers. These are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

PPI Dendrimer – PPI or Poly (Propylene Imine)/ Poly (Propylene Amine) is one of the oldest known dendrimer developed initially by Vogtle. Its core structure is based on diamino butane with primary amines as end groups and tertiary propylene amines as interior. Thus, these dendrimers are also sometimes referred to as "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane. PPI dendrimers are commercially available up to G5, and has found widespread applications in the field of material science and biology. These are widely available as AstramolTM.

Tecto Dendrimer – These are composed of a core dendrimer, surrounded by other dendrimers, each one of which perform a specific function leading to a smart therapeutic system which can simultaneously diagnose the diseased state and deliver API to the recognized diseased cell.. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state, drug delivery, reporting outcomes of therapy.

Liquid crystalline Dendrimers – These are highly-branched oligomer or polymer of dendritic structure containing mesogenic groups that can display mesophase behaviour. They consist of mesogenic (liquid crystalline) monomers, e.g. mesogen functionalized carbosilane dendrimers.

Multilingual Dendrimers – These dendrimers consists of multiple copies of a particular functional group on their surface.

Chiral Dendrimers – The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to the chiral core. Their potential use as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetric synthesis has been recognized.

Hybrid Dendrimers – These are hybrids (block or graft polymers) of dendritic and linear polymers having characters of both. Hybrid dendrimers are obtained by complete monofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer; provide structurally diverse lamellar, columnar, and cubic self organized lattices that are less readily available from other modified dendritic structures.

Amphiphilic Dendrimers – These are composed of two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

Micellar Dendrimers – These are unimolecular micelles of water soluble hyper branched polyphenylenes micelles.

Peptide Dendrimers – These dendrimers consists of amino acids as branching or interior unit. It is a dendron like molecular construct based upon a polylysine skeleton. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, such as in vaccine and diagnostic research.

Frechet-Type Dendrimers – It is a more recent type of dendrimer developed by Hawker and Frechet based on polybenzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface fictionalization, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media.

Synthesis of Dendrimers [5] [9]

(1) Divergent growth method – This method was first introduced by Tomalia. In this method, the growth of dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, lead to the first generation dendrimers. This process is repeated until the dendrimer of the desired size is obtained. By this approach the first synthesized dendrimers were polyamidoamines (PAMAMs), also known as starbust dendrimers.

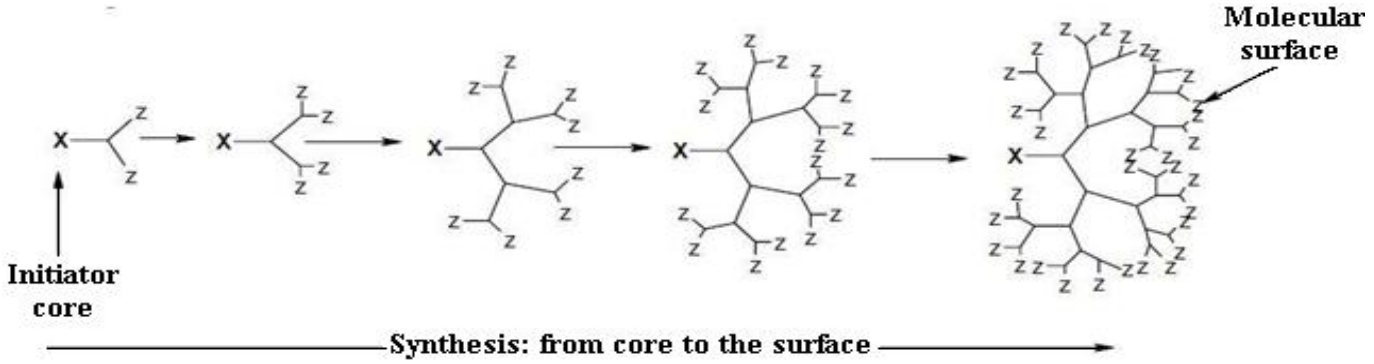

Figure 2: Divergent synthesis of dendrimer : Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups.

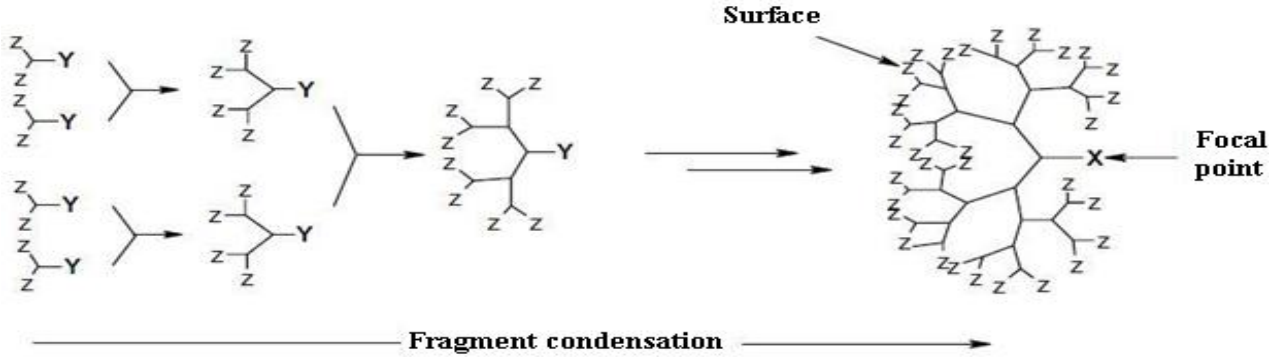

Figure 3: Convergent synthesis of dendrimer – Synthesized inwards by gradually linking surface units together with more branching points.

(2) Convergent Dendrimer Growth – Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. Convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule [5].

An advantage of convergent growth over divergent growth is that purification is done after each step whereas in divergent method since the reactant and product remains same it is difficult to purify by chromatographic technique.

(3) Double Exponential and Mixed Growth – In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.

(4) Hypercores and Branched Monomers Growth – This method involves the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation Dendrimers.

Mechanism of drug delivery through dendrimers

The well-defined 3D structure and many functional surface groups, drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. 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 (prodrug). There are broadly

two mechanisms for drug delivery.

I. Drug molecules can be physically entrapped within the dendritic structure;

II. Drug molecules can be covalently linked onto the dendrimer surface (or) other functionalities to produce dendrimer drug conjugate.

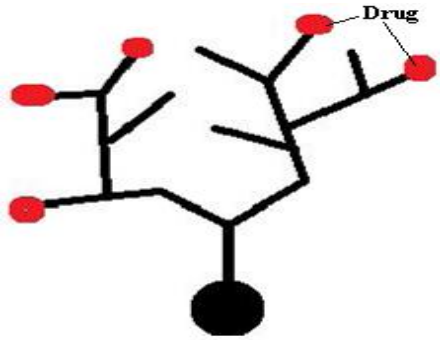

Fig 4: A dendrimer molecule with drug molecules
Loaded at terminal surface of branches

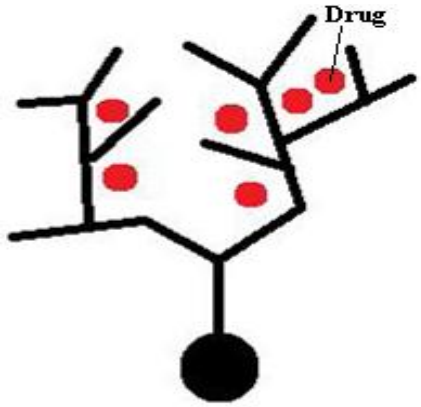

Fig 5: A dendrimer molecule with terminal drug molecules
Encapsulated within branches

A dendrimer of higher generations consists of shell. A shell consists of a central core and alternating two layers of monomers around it. Amines constitute the central core which may sometimes be replaced by sugar. All core molecules have multiple and identical reaction site. Amine is the simplest core molecule present with three functional sites. The surface of all full generations consists of multiple amines, while the surface of the half generations consists of multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components [5].

Applications

There are now more than fifty families of dendrimers, each with having unique properties since the surface, interior and core can be tailored to different sort of applications. Many potential applications of dendrimers are based on their unparalleled molecular uniformity, multifunctional surface and presence of internal cavities. These specific properties make dendrimers suitable for a variety of high technology uses including biomedical and industrial applications which are as follows [10].

A. Pharmaceutical applications

The dendrimers are used as targeted moiety for various cytotoxic drug substances. Apart from that dendrimers also used as active moiety to treat various diseases, that is why dendrimers have gained popularity in pharmaceutical field in recent days.

1) Dendrimers in biomedical field

The dendritic polymer has advantage in biomedical applications. These dendritic polymers are analogous to protein, enzymes and viruses and can be easily functionalized. Dendrimers and other molecules can either be attached to periphery or can be encapsulated in their interior voids. The dendrimer should possess certain qualities for its utility as biological agents. The dendrimer should be non toxic, non immunogenic, bio permeable, able to target specific structure.

Due to specific synthesis, Polyamidoamine (PAMAM) dendrimers possess the interesting properties, which distinguish it from classical linear polymers and are the most studied starburst macromolecule. PAMAM dendrimers can also be used to target tumour cells. Targeting groups can be conjugated to the host dendrimers surface 20 to allow the imaging agent to bond selectively to specific site such as receptors on tumour cell to improve detection. Cisplatin was complexed to the surface groups of a carboxylate-terminated PAMAM dendrimer which led to a tenfold increase in the solubility of cisplatin compared to the free drug. It was also found that the use of lower molecular weight dendrimers with denser interiors and ellipsoidal, flattered or elongated shaped may result in improved dendritic MRI contrast agents [11].

2) Dendrimer as magnetic resonance imaging contrast agents

Dendrimer based metal chelates act as a magnetic resonance imaging contrast agent. Dendrimers are highly suited and used as image contrast media because of their

properties. Many tests carried on dendrimers have shown that these are stronger contrast agent than conventional ones. They can improve visualisation of vascular structure in magnetic resonance angiography (MRA) of the body. Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged enhancement with a half-life of 200 min compared to 24 min for monovalent gadolinium agent. This prolonged enhancement time is extremely useful for 3D time-of-flight MR angiography. In the recent study, it was found that the molecular size of a dendrimer-based MRI agent altered the route of excretion. Contrast agents having molecular weight less than 60 kDa were excreted through kidney being potentially suitable as functional renal contrast agents. Larger sized and hydrophilic contrast agents were found better for use as blood pool contrast agent. Larger hydrophilic agents were useful for lymphatic imaging. Finally, these dendrimer based MRI agents were recognized by the pharmaceutical industry which results in various commercial developments.

3) Dendrimers in Antitumor Therapy

Dendrimers molecule has found use as diagnostic reagent for tumour imaging by magnetic resonance imaging and as contrast agent; by varying the size and hydrophilicity and by combining with tumour targeting antibodies, these compounds can be used for a range of specific imaging purpose. The drug used should be non-toxic, under nonirradiative condition, thus acting as prodrug when not irradiated. Dendrimers containing photosensitises such as 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for photodynamic therapy (PDT) of tumorigenic keratinocytes. The administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue were involved in cancer treatment. Also, glycodendrimer constitute an important class of therapeutic molecules. The dendrimers were investigated with the purpose of producing a drug that would interact with carcinoma derived Tantigen- binding receptors to interfere with carcinoma growth. This type of Glycodendrimer reacted in a generation dependent way with monoclonal antibodies against the T-antigen with higher generation having higher affinities. The therapeutic uses of dendrimers may be within the cancer field where numerous examples of targeting tumours for diagnostic purpose have been described and where it is possible to define a cancer specific cell surface component that can be targeted [12].

4) Dendrimers in gene transfection

Gene transfection is a direct approach where DNA is coupled to a nanoparticle of inert solid, which is then directly targeted to the cell nucleus. This process has become much valuable tool in molecular biology for studying mutations and regulation processes of genes or inducing over expression of desired proteins [13].

The ideal vector for transfection should have high efficiency, non-immunogenic, non-toxic, either bio-degradable or excretable and has long blood circulation time. PAMAM dendrimers were the first found to be tested as genetic material carriers. Amino terminated PAMAM or PPI dendrimers have been reported as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus.

A transfection reagent called SuperFectTM consisting of activated dendrimers is commercially available. These activated dendrimers can carry a larger amount of genetic material than viruses. SuperFect–DNA complexes are characterized by high stability and provide more efficient transport of DNA into the nucleus than liposomes. The high transfection efficiency of dendrimers may be due to their well-defined shape and the low pKa of the amines (3.9 and 6.9) which permit the dendrimer to buffer the pH change in the endosomal compartment. PAMAM dendrimers functionalized with cyclodextrin showed luciferase gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and cyclodextrin. It should be noted that dendrimers of high structural flexibility and partially degraded high-generation dendrimers (i.e., hyper branched architectures) appear to be better suited for certain gene delivery operations than intact high-generation symmetrical Dendrimers [1].

5) Dendrimers as Biomimics

Dendrimers having their well defined macromolecular dimensions and compartmentalised structure are ideal mimics for a wide variety of biomolecules. The commercially available dendrimers provide possibility to create micro environments. PAMAM dendrimers with their network consisting of numerous mixed tertiary amines. Dendrimers have ability to expose the multivalent surface for increased

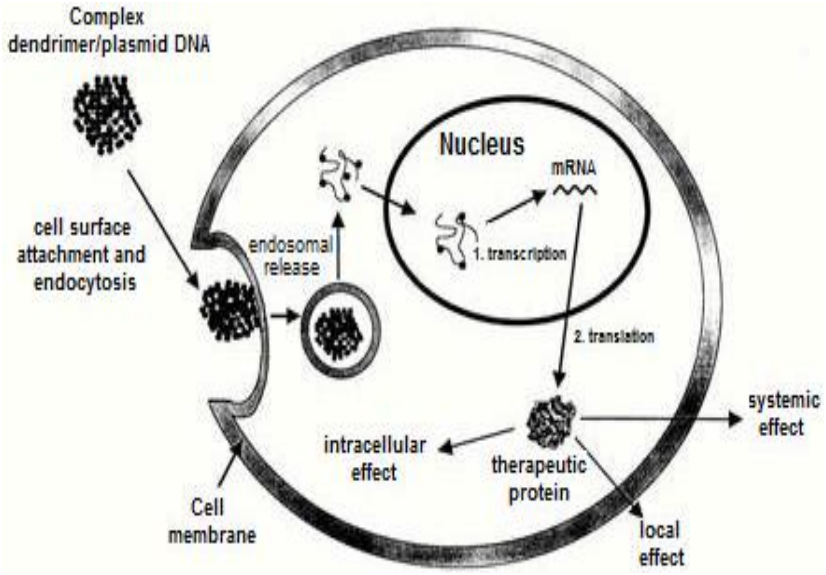

Figure 6: Dendrimers involved in gene transfection [13] – Dendrimer complexed with plasmid DNA is targeted to the cell nucleus, which produces therapeutic protein and provides intracellular, local and systemic effect.

binding of biomolecules. Also, dendrimers have ability to create a micro environment inside the dendrimer, which makes artificial catalytic sites or cavities possessing different properties for construction of enzyme mimics.

Dendrimer molecules are characterized by zones of different density, depending upon the rigidity or the conformational mobility of their scaffold; they combine dense and less dense areas. They are flexible and have cavities to accommodate solvent to act as host compounds for guest substance. By using dendrimers more favorable qualities compared to naturally occurring proteins can be obtained. More densely packed structure compared to the natural proteins, for example certain peptide based dendrimer system show a significant increased resistance towards proteases. The dendrimer is also used as a building block to mimic a non-globular collagen structure, showing that dendrimers, although being mostly globular shaped, may be used as mimics of non-globular structures. Dendrimers may also mimic numerous protein based receptors utilized in nature for specific biological recognition. Glycomometics are synthesized analogous carbohydrate whose structure has been simplified and modified, and is an active ingredient, which can be used for treatment of chronic inflammatory ailment such as rheumatism, dermatitis and psoriasis.

6) Dendrimers in targeted drug delivery

Targeted drug delivery is a process of introducing medicine to a patient in a manner that increases the concentration of medication in particular part of body. A certain amount of therapeutic agent is delivered for a prolonged period of time to the targeted diseased area within the body, which helps to maintain the required plasma and tissue drug level. Dendrimers have multifunctionality and high potential for drug delivery applications as they possess high density and wide variety of functional groups on its surface. Its well defined molecular structure, segmental spherical construction of dendrimers offers an interesting architecture for dendrimers. If one of these segments is attached with active drug molecule, the other can be highlighted as targeting group. Due to this double functional group, the plasma level of the drugs will stay at desired level for longer time period and increase its Pharmaceutical efficiency. Generally, the therapeutic efficiency of drug is diminished due to low bioavailability, insolubility, toxicity and the decomposition of drug under biological circumstances. Using Dendrimers containing targeting moieties onto conjugated drug molecule, the above shortcomings can be overcome [14].

7) Dendrimers in drug delivery

Drug molecule can be loaded in the interior and also to the surface of dendrimers. Encapsulation of the well known anticancer drug cisplatin within PAMAM dendrimers gave conjugates which can slow down release and higher accumulation in solid tumours and it has low toxicity than free cisplatin. The encapsulation of silver salts within PAMAM dendrimers produces conjugates that can exhibit slow silver release rates along with antimicrobial activities against different gram positive bacteria. Dendrimers are highly soluble and compatible, due to which, solubility of drug in body can be increased. As dendrimers is water soluble and capable of binding and solubilising acidic hydrophobic molecules with antifungal and antibacterial properties. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation. Therapeutic agents can be attached to a dendrimer to direct the delivery. For example, dendrimers in boron neutron capture therapy (BNCT)

8) Dendrimers in transdermal drug delivery

In order to improve the effectiveness of drug, transdermal drug delivery system has come into existence long back. Drug delivery through skin to achieve a systematic effect of drug is known as transdermal drug delivery. Transdermal delivery provides controlled, constant administration of the drug which extends the activity of drug having short half life through the reservoir of drug present in the delivery system and its controlled release characteristics. The drug which is to be delivered should have low melting point, should be potent, having short half life and non- irritating. PAMAM dendrimer complex with Non Steroidal Anti-inflammatory Drugs such as ketoprofen, diflunisal which are very effective in treatment of acute and chronic rheumatoid and osteoarthritis, could improve the drug permeation through the skin as penetration enhancers. The model drugs ketoprofen and diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies.

9) Dendrimers in oral drug delivery

Oral drug delivery is the most popular and has received more attention in the pharmaceutical field because of ease of production, low cost, convenience of ease of administration and flexibility in designing of dosage. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and the patient, the length of the therapy and properties of the drug. The controlled release system for the oral use are mostly solids based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug. One important advantage of oral drug delivery is less fluctuating plasma drug level is maintained with controlled drug delivery systems, because the drug is slowly released from the dosage continuously and maintains the constant blood level. Along with the merits there are some demerits of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes. D'Emanuele et. al., 2003 investigated the effects of dendrimer generation and conjugation on cytotoxicity, permeation and transport mechanism of PAMAM dendrimer. As the concentration and generation increased, the increase in cytotoxicity and permeation of dendrimers resulted. Reduction in cytotoxicity was observed by conjugation with lauryl chloride.

10) Dendrimers in ocular drug delivery

The topical application of active drugs to the eye is the most prescribed route of administration for the treatment of ocular disorders. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. An ideal ocular drug delivery system should be non-irritating, biocompatible, sterile, isotonic and biodegradable. The recent problems for ocular drug delivery focus on increasing the residence time of pilocarpine in the eye was overcome by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface modified dendrimers were predicted to enhance pilocarpine bioavailability.

11) Dendrimers in pulmonary drug delivery

Dendrimers have also been reported for pulmonary drug delivery as well. In one of the studies, by measuring plasma anti-factor Xa activity using PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin, and by observing prevention efficacy of deep vein thrombosis in a rodent model, it was observed that G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40% while G2.5 PAMAM half generation dendrimers containing negatively charged carboxylic groups had no effect. So the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery.

12) Dendrimers as solubility enhancers

Inclusion of drug with cyclodextrin and urea for the enhancement of solubility is an oldest approach, so scientist uses dendrimers as solubility enhancer in recent years. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers that are soluble in water are capable of binding and solubilising small acidic hydrophobic molecule with antifungal or antibacterial activities. Dendrimers having a hydrophobic core and a hydrophilic surface layer have been termed unimolecular micelles. Dendrimer possess unimolecular micelle and do not possess a critical micelle concentration. These characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure not have a critical micelle concentration. This characteristic offers the opportunity to poorly soluble drugs by encapsulating them within the dendritic structure at all concentrations of dendrimer. These carriers offer the opportunity to enhance the oral bioavailability of problematic drugs. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters. A hydrophilic–hydrophobic core shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-flurouracil, a water-soluble anti-tumor drug. Propranolol, conjugated to surface-modified G3 PAMAM dendrimer, the solubility of propranolol increased by over two orders of magnitude. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

B. Non-pharmaceutical applications

1) Dendrimers as catalysts/enzymes

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. These types of catalyst are an intermediate between heterogeneous and homogeneous catalyst which can be recovered easily from the reaction mixture by ultra filtration methods. Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Dendrimers have multifunctional surface with active catalytic site. Insoluble materials can be encapsulated such as metals, and transport them into a solvent in interior of dendrimer. Some popular dendrimeric catalysts are terminated soluble polycarbosilane dendrimers in diamino arylnickel (II) complexes [10] [11].

2) Dendrimers for additives, printing inks and paints

Dendrimers can be used in toners material with additives which require less material than their liquid counterparts. Xerox Corporation patented a dry toner compound dendrimers as charge enhancing species in the form of an additive. Using additives in printing inks, dendritic polymers ensure uniform adhesion of ink to polar and non-polar foils. Here, first the hyper branched compounds attach themselves to the pigment particles and there are still large numbers of functional groups remaining to give adhesion to the surface of the foils.

Dendritic polymers used in polyurethane paints impart surface hardness, scratch resistance, chemical resistance, light fastness, weathering resistance as well as high gloss, because of which they are used in furniture and automotive industries. Use of Dendrimer additives in the composition of the invention is effective for altering the surface characterization of thermo plastic resin after moulding. One of example for this is polycarbonates, which are widely used as an engineering thermoplastic for providing a unique combination of toughness, stiffness, high softening temperature and processibility.

3) Dendrimers as a separating agent

A study of variety of compounds synthesized to determine suitability for enhancing boron rejection by reverse osmosis and nanofilteration membrane to separate boron from sea water has been developed. For separation, compound must have amphiphile chemical structure and form micelle in aqueous solution. As a new compound dendrimers with a high density of functional moiety, is able to form micelle structure which can be easily separated and recovered by ultra filtration membrane. These micelles provide high functional density at the surface of the particle, high surface area and ease of separation for isolation and regeneration of the compound. It was found that unmodified commercial dendrimeric compounds containing amine and hydroxyl groups are generally more effective for boron absorption. Polyamidoamine (PAMAM) dendrimers are used as chelating

agents for the removal of certain metal ions from waste water and from contaminated soil. Other modified chelating PAMAM and poly (propyleneimine) dendrimer are also reported to be good ligands for a various hard metal cations, or can be described as nanosponges for the removal of polycyclic aromatic hydrocarbons and other particles.

4) Industrial Processes

In recent years, the dendrimers are also gaining the popularity in many industries as par their vast applications. Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. Cooper et. al., 1997 synthesized fluorinated dendrimers, soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from water into liquid CO_2. This may help develop technologies in which hazardous organic solvents are replaced by liquid CO_2.

Future prospects of dendrimers

Although dendritic polymers only have a short history of nearly two decades, the amount of patents and papers is increasing every year, which makes continuous progresses on their applications in both academic researches and industry processes. However, there are very few pharmaceutical products using dendrimers as carriers which are currently available in the market, dendrimer technology holds great potential to add value to pharmaceutical products.

Use of dendrimers as topical microbicide products is marching ahead with positive results and, in the process, leading the field for HIV prevention. It is expected that dendrimer technology will find increasing applications in commercial products of all types in coming years. In the future, more attention should be paid to improving the synthesis of novel dendritic polymers and inventing the new methods for membrane formation with dendritic polymers. In particular, future developments will focus on the following aspects:

a. Reducing the synthesis costs of dendrimers so that they can be extensively applied in membranes and other fields.
b. Enlarging the application of the membranes from hyperbranched polymers to the fields of resources and environments, such as fuel cell-membranes, liquid separation membranes.
c. Exploiting the new applications of dendritic polymers in the other fields of membrane. As a general rule, the structure and properties of membranes from dendritic polymers should also be correlated.

Confidence in the use of dendrimers for drug delivery was boosted in May 2008, with the announcement of positive clinical trial results by Starpharma Holdings Limited, demonstrating that its topical vaginal microbicide gel

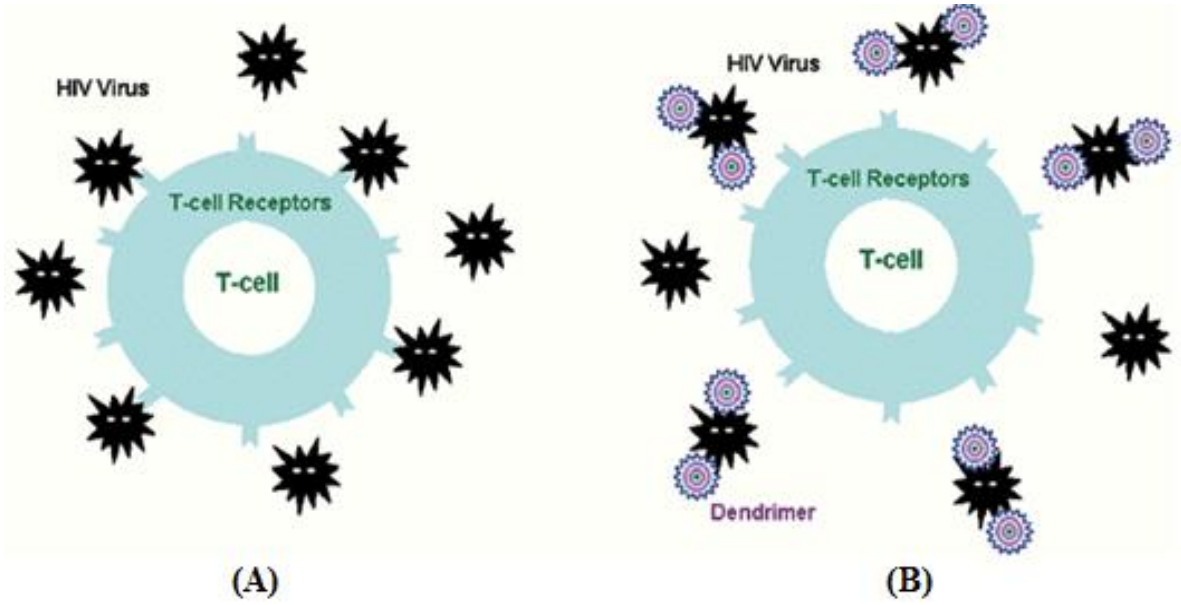

Figure 7: Schematic mechanism of a dendrimer as a topical vaginal microbicide [13] [15] – HIV viral particles (black) attach to T-cell receptors on the surface of the T-cells (blue) as an initial step in infection without dendrimer application (A); Dendrimers bind to the surface of HIV particles and block attachment, reducing or preventing infection with dendrimer application (B).

product (3% SPL7013 Gel) was found to be safe and well tolerated in sexually abstinent women when administered twice daily for a 14-day treatment period. In this case, dendrimers act by binding to the gp120 glycoprotein binding sites on the HIV virus, which prevents the virus from attaching to the T-cells, thereby blocking infection [13] [15].

This topical vaginal microbicide is designed to prevent transmission of sexually transmitted infections, including HIV and genital herpes, and uses dendrimers as an active agent. This was the first dendrimer-based product to be approved by regulatory authorities for human clinical testing under an investigational new drug application for prevention of genital herpes. It was reported that no participants showed unto ward effect from using the fourth-generation polylysine dendrimer-based gel. In addition, no absorption of the active agent used in the gel was found in the systemic blood circulation after vaginal topical application. Vaginal microflora was also found to be unaffected after Viva Gel (Starpharma) treatment. Currently, the topical vaginal gel is in Phase II human clinical trials.

Other dendrimer based products that are in process of reaching commercial reality include Avidimers (Avidimer Therapeutics) for cancer prevention and treatment and gadolinium-based MRI contrast agent. Starpharma, in collaboration with its US-based wholly owned company Dendritic Nanotechnologies (Mount Pleasant, MI), recently announced the commercial launch of its Priostar dendrimer-based technology research product called NanoJuice Transfection Kit in addition to the Starburst and Priostar-based dendrimer family. These will be useful for transfection of DNA into the variety of difficult-to-transfect cells. As the number of commercial applications of dendrimer technology increases, acceptance and confidence in this novel technology will gain strength for use in future products.

CONCLUSION

Dendritic polymers are expected to play a key role as enabling building blocks for nanotechnology during the 21st century, just as the first three traditional architectural classes of synthetic polymers have so successfully fulfilled critical material and functional needs in the plastics age during the past half century. The controlled shape, size, and differentiated functionality of dendrimers; their ability to provide both isotropic and anisotropic assemblies; their compatibility with many other nanoscale building blocks such as DNA, metal nanocrystals, and nanotubes; their potential for ordered self-assembly; their ability to combine both organic and inorganic components; and their propensity to either encapsulate or be engineered into unimolecular functional devices make dendrimers uniquely versatile amongst existing nanoscale building blocks and materials. Dendritic polymers, especially dendrons and dendrimers, are expected to fulfill an important role as fundamental modules for nanoscale synthesis. It is from this perspective that it is appropriate to be optimistic about the future of this new major polymer class, the dendritic state.

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