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DENDRIMERS: NOVEL DRUG NANOCARRIERS

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ABSTRACT

Dendrimers are unique class of the polymer which is characterized by its extensively branched 3D structure that provides a high degree of surface functionality and versatility. Many drugs used in various therapies are facing difficulties like toxicity or nonspecific targeting. New delivery technologies could help to overcome this challenge. Nanostructures with uniform and well-defined particle size and shape are of eminent interest in biomedical applications because of their ability to cross cell membranes and to reduce the risk of premature clearance from the body. Hydrophobic drugs can be complex within the hydrophobic dendrimers interior to make them water-soluble or drugs can be covalently coupled onto the surface of the dendrimers. Structural features of this nanomolecule can be effectively modified for drug delivery in the field of pharmaceutical sciences and biotechnology. Present review deals with various applications along with relevant examples of dendrimers in brief.

INTRODUCTION: Development of completely bioavailable dosage form of a drug is always being challenge to the research scientist. Various approaches have been used to enhance the therapeutic effect of the drug with less toxicity these include improvement of solubility, microspheres, microemulsion, iontophoresis and sonophoresis, liposomes etc. In the last decade, the field of preparation of materials with low dimensionality and the investigation of their properties gained more and more importance. Nanotechnology has been applied on various platforms such as Targeted and controlled drug delivery, Medical devices, Cell/tissue engineering, Gene delivery, Molecular-tags, Biosensors, bioanalysis [1-6].

Nanoparticles have unusual properties that can be used to improve drug delivery. Where larger particles would have been cleared from the body, cells take up these nanoparticles because of their size. Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm Dendrimers is the class of synthetic polymeric macromolecule which play important role in emerging nanotechnology. It is described as highly branched macromolecule, which provides a high degree of surface functionality and versatility. It is derived from the Greek words *Dendron* (tree) and *meros* (part) [7].

It possess a 3-D features that resemble a tree. Their syntheses are attributed to Vogtle group [8] in the late 1970s, followed by the work of Tomalia *et al*., [9] in the early 1980s. Two major strategies have evolved for dendrimer synthesis: The first, divergent method in which growth of a dendron originates from a core site in which the dendrimer grows outwards from the core, diverging into space as shown in **fig. 1**. The second method is the convergent growth process which works inwards by gradually linking surface units together as given in **fig. 2**.

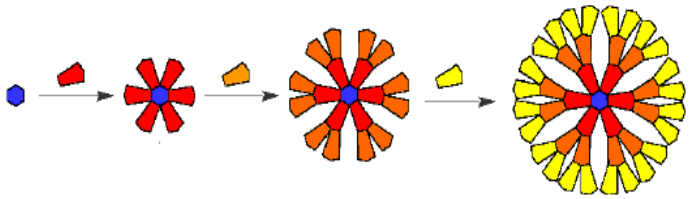

FIG. 1: DIVERGENT GROWTH METHOD

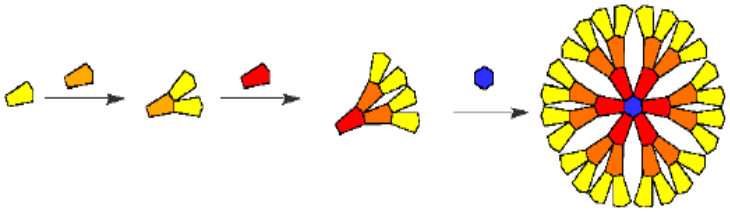

FIG. 2: CONVERGENT GROWTH METHOD

When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. [10-13] 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.

It possesses three distinguished architectural components as shown in **fig. 3** [14-16].

1. An initiator core.
2. Interior layers (generations) composed of repeating units, radically attached to the interior core.
3. Exterior (terminal functionality) attached to the outermost interior generations.

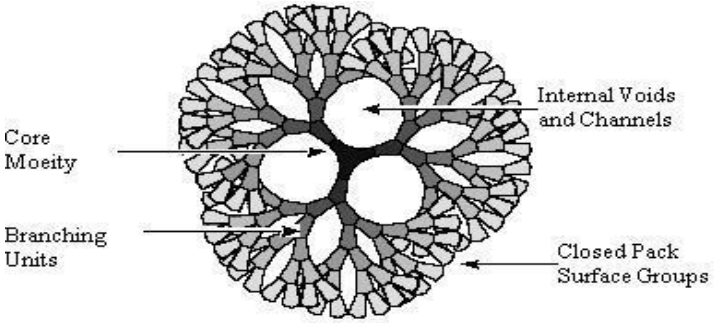

FIG. 3: THE DENDRITIC STRUCTURE

Dendrimers are core-shell nanostructures with precise architecture and low polydispersity, which are synthesized in a layer-by-layer fashion (expressed in 'generations') around a core unit, resulting in high level of control over size, branching points and surface functionality. Dendritic macromolecules tend to linearly increase in diameter and adopt a more globular shape with increasing dendrimer generation. When dendrimers condense into globular structures, their many termini become fixed into an outwards orientation and also form a densely packed, membrane-like surface.

This structural arrangement provides numerous attachment points for covalent conjugation of bioactive molecules on the surface as well as enclosed cavities for occlusion of guest molecules within the dendrimers. Dendrimers are of great interest as carriers of functional groups because of their highly branched monodisperse structures in nanometer scale, the size of dendrimers can be carefully controlled during synthesis. Compared to polymers dendrimers reveal varied physical properties such as viscosity which tends to increase maximum at approximately the fourth generation and then declines, flexibility due to the extensive covalent bond networks, and density distribution, narrow molecular weight distribution, specific size and shape characteristics, and a highly-functionalized terminal surface.

The ability to tailor dendrimer properties to therapeutic needs makes them ideal carriers for small molecule drugs and biomolecules. The major properties of dendrimers are;

1. Nanoscale container properties (i.e., encapsulation of a drug), Encapsulating in that void space reduces the drug toxicity and facilitates controlled release.
2. Nano-scaffolding properties (i.e., surface adsorption or attachment of a drug), Surfaces that may be designed with functional groups to augment or resist trans-cellular, epithelial or vascular biopermeability.
3. Biocompatibility, positive biocompatibility patterns that are associated with lower generation anionic or neutral polar terminal surface groups as compared to higher generation neutral nonpolar and cationic surface groups.
4. None or low-immunogenicity associated with most dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG).
5. Surface groups that can be modified to optimize biodistribution; receptor mediated targeting, therapy dosage or controlled release of drug from the interior space.
6. Ability to arrange excretion mode from body, as a function of nanoscale diameter [17-24].

The focus of this review is to discuss various drug delivery applications of dendrimers in detail.

Dendrimers for Cancer Treatment: Millions of humans from all age groups are affected by the cancer. Most of the current chemotherapeutic agents on the market are the low molecular weight which makes them easily excreted, hence a higher concentration is ultimately required, and additionally, these drugs when administrated alone, lack specificity and cause significant damage to noncancerous tissues. This results in serious, unwanted side effects [25].

Therapeutic agents can be internalized into the void space between the periphery and core, or covalently attached to functionalized surface groups .Dendrimers are small enough to slip through tiny openings in cell membranes and retention effect that improves the delivery of macromolecules to tumors, targeting moieties bound to the dendrimer surface can be used to preferentially treat cancer cells with certain over-expressed receptor targets [25]. Dendrimer-drug conjugates generally consist of an antineoplastic agent covalently attached to the peripheral groups of the dendrimer. This method offers distinct advantages over drug-encapsulated systems. Multiple drug molecules can be attached to each dendrimer molecule and the release of these therapeutic

molecules is partially controlled by the nature of the linkages. Mechanism of drug delivery includes Dendrimer lipid bilayer interaction. It was proposed that dendrimers shape and charge play a part in forming dendrimer-lipid vesicles by removing individual lipid molecules from the membrane. Dendrimers have charged group the interaction between these groups with the cell membrane disrupt the cell membrane. The ratio of lipid head groups (L) in contact with the dendrimer surface to the number of dendrimer peripheral end groups (P) seems to be a determining factor in hole formation [26].

The concept of dendrimer architecture and membrane bilayer hole creation was broadened to a range of linear and Dendritic polycationic polymers commonly investigated for drug delivery applications.[27] Although membrane permeability may play a role in the cellular uptake of certain dendrimers conventional modes of endocytotic internalization are attributed to the uptake of many dendrimers [28]. With the increase of molecular weight of the drug, dendrimer-drug interaction, the hydrodynamic volume increases causing longer circulation time and slower elimination of drug so cytotoxicity levels are lowered and dosage can be decreased [29].

There are numerous examples of dendrimer mediated targeted drug delivery: Poly(glycerol succinic acid) dendrimers, or PGLSA dendrimers, were investigated as delivery vehicles for camptothecins, In a preliminary study reported by the Grinstaff group, G4-PGLSA dendrimers with hydroxyl (G4-PGLSA-OH) or carboxylate (G4-PGLSA-COONa) peripheral groups were used to encapsulate 10-hydroxycamptothecin (10-HCPT) for delivery to cancer cells [30]. The G4-PGLSA-OH -10-HCPT solution precipitated upon standing after mixing; the more water-soluble G4-PGLSA-COONa dendrimer was used to improve overall solubility and 10-HCPT was successfully encapsulated. Upon exposure to MCF-7 human breast cancer cells, unloaded dendrimer showed no cytotoxic effects, while 10-HCPT-encapsulated dendrimers led to significant cytotoxicity. An alternative triblock structure PEG 3400 core was introduced to the G4-PGLSA dendrimer to afford (G4-PGLSA-OH) 2-PEG3400. A 20-fold increase in 10-HCPT water solubility was observed following encapsulation. The conclusions drawn from these two studies led to the selection of G4-PGLSA-COONa dendrimer as a delivery vehicle for 10-HCPT and 7-butyl-10-aminocamptothecin (BACPT), a highly potent lipophilic camptothecin derivative. The release profile of 10-HCPTencapsulated G4-PGLSA-COONa showed full release of the drug within approximately 6 h, suggesting that the delivery system may be best utilized.

Uptake studies showed that dendrimer-encapsulated 10-HCPT was internalized much faster than free drug, with 16-fold intracellular concentrations at 2 h and 8-fold intracellular concentrations at 10 h. Drug delivered via the dendrimers also showed longer retention time in the cell, with 50% of delivered 10-HCPT present in the cell after 30 min, compared to 35% of free drug. Thus, delivered camptothecins was attributed to enhanced uptake and retention [26, 31-32].

Paclitaxel was conjugated to PEG or G4-PAMAM. Both PEG and PAMAM increased the aqueous solubility of paclitaxel (0.3 µg/mL) dramatically to 2.5 mg/mL and 3.2 mg/mL respectively. Upon exposure to human ovarian carcinoma A2780 cells, free paclitaxel accumulated in the cytoplasm near the plasma membrane. The polymer conjugates tended to distribute intracellularly in a more homogenous fashion compared to free drug. The availability of a drug is dramatically influenced by the architecture of its polymer conjugate [26, 33].

Tooru Ooya and *et al*., reported the solubility enhancement of Paclitaxel by using dendrimers of Oligo(ethylene glycol) methacrylate (OEGMA) and PEG 400. They have synthesized five different types of dendrimers as Poly(OEGMA), five- arm star poly (OEGMA) Polyglycerol dendrimers (dendri PGs) with generation 3, (G-3), 4 (G-4) and 5 (G-5) by two

different methods of synthesis [34, 35]. The ability to enhance the paclitaxel solubility at 10 wt % concentration was in the increasing order: G-5, G-4, G-3 dendrimers, star poly (OEGMA) and linear poly (OEGMA). Poly (OEGMA) increased the paclitaxel solubility, but a much more significant effect was observed with the five-arm star poly (OEGMA), even though the molecular weight of the arm segment in the star poly (OEGMA) was similar to that of poly (OEGMA).

Thus, the paclitaxel solubility in 10 wt % star poly (OEGMA), in G-3, G-4 and G-5 was 130, 270-, 370- and 430-fold higher respectively, than the paclitaxel solubility in water.

This result supports the hypothesis that increasing the density of PEG400 chains or ethylene glycol units is a key factor in enhancing the solubility of paclitaxel. From this point of view, the dendritic architecture of the polyglycerol dendrimers can be expected to further increase the density of the ethylene glycol units, the star and dendritic polymers consisting of ethylene glycol units are expected to be useful for both oral and parenteral delivery of paclitaxel and other poorly water-soluble drugs [36].

Etoposide can be encapsulated in a star polymer composed of amphiphilic block copolymer arms. The core of the star polymer is polyamidoamine (PAMAM) dendrimer, the inner block in the arm is lipophilic poly (epsilon-caprolactone) (PCL), and the outer block in the arm is hydrophilic poly(ethylene glycol) (PEG). The star-PCL polymer was synthesized first by ring-opening polymerization of epsilon-caprolactone with a PAMAM-OH dendrimer as initiator. The PEG polymer was then attached to the PCL terminus by an ester-forming reaction. A loading capacity of up to 22% (w/w) was achieved with a hydrophobic anticancer drug. A cytotoxicity assay demonstrated that the star-PCL-PEG copolymer is nontoxic in cell culture. This type of block copolymer can be used as a drug delivery carrier [37].

Dendrimers for Ocular Delivery: The anatomy, physiology, and biochemistry of the eye are one of the most complex.[38] Many drug delivery systems are utilized for ophthalmic treatment such as eye drops, ointments, inserts, implants, colloids, and suspensions.[39] However, all of these systems have their own advantages and disadvantages, intraocular bioavailability of topically applied drug is poor which ultimately responsible for ineffective treatment. Nanotechnology for ocular delivery drug delivery to eye is an emerging concept offers a more accurate targeted delivery and controlled drug release of drug. Size and versatile properties of the dendrimers can be effectively utilized as drug delivery system. Dendrimers are especially ideal for synthesizing hydrogels and are more similar to living tissue than any other synthetic compound. By adding polyethylene glycol or PEG groups to the dendrimers, these hydrogels have applications including cartilage tissue production and for sealing ophthalmic injuries [40]. These compounds can be utilized to control the release of dendrimers.

Th. F. Vandamme and L. Brobeck prepared Poly (amidoamine) dendrimers for ocular delivery of pilocarpine nitrate and tropicamide. PAMAM dendrimers are liquid or semi-solid polymers and have a number of amine, carboxylic and hydroxyl surface groups which increases with the generation number (G0, G1, G2, etc.) The unique architecture of PAMAM dendrimers, polymers is able to solubilize strongly and poorly water soluble drugs [41, 42]. This diversity of structure is mainly responsible for the types of interaction between dendrimers and various chemical or biological systems.

Functional groups as carboxyl, hydroxyl and amine establish electrostatic and hydrophobic interactions and hydrogen bonds with the underlying surface. Interaction between dendrimers and the surface of the cornea can lead to a structure with more rigid behavior and trapping some of the instilled solution. The release of this trapped solution will be slower because the solutes have to diffuse through this macromolecular

structure. To make it easier to visualize the fluorescent solutions on the cornea, fluoresce in was added to the PAMAM dendrimer solutions. PAMAM dendrimers demonstrated physicochemical characteristics (pH, osmolality, viscosity) which are compatible with ocular dosage form formulations. In addition to size and molecular weight, charge and molecular geometry of bioadhesive dendrimers also influence ocular residence time and the increased bioavailability of drugs incorporated in eye drops [43].

The repair of wounds after traumatic or surgical injury is of significant of importance. Corneal wounds arise from surgical procedures (e.g., transplants, incisions for cataract removal and intraocular lens implantation, laser-assisted *in situ* keratomileusis), infections (ulcers), and traumatic injury (lacerations, perforations). Currently, these wounds are repaired using nylon sutures, but this technique is not ideal because the suture material does not actively participate in healing, and the procedure is inherently invasive. Therefore, alternative strategies using adhesive polymers have been used [44]. Duan and Sheardown cross-linked collagen with multi-functional dendrimers. PPI octa amine dendrimers (G2) to generate highly cross-linked collagen hydrogels with mechanical properties that would make it appropriate for use as corneal tissue engineering scaffold [45]. Grinstaff has developed a set of dendrimeric adhesives composed of dendrimers of different generations (G1, G2 and G3) combined with PEG, glycerol, and succinic acid for finding application in the repair of corneal wounds [46].

Dendrimers for Oral Delivery: Oral drug-delivery system has been the dominant route for many years because of its significant advantages. It is by far the most convenient administration route with good patient compliance, especially in the patient's opinions. Along with these benefits, there are also some defects of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes [47, 48]. Transport of dendrimers throughout epithelial part of gastrointestinal tract depends upon its characteristics [49]. Packaging a drug in a dendrimer host not only makes it soluble but also allows it to bypass the transporter protein that would normally stop it from being absorbed in the intestines after it has been taken orally [50].

Mohammad Najlah and *et al.,* have studied the use of G0 PAMAM dendrimers as drug carriers using naproxen as a prodrug *in vitro*. Direct amide linkage of naproxen to the G0 dendrimer produced prodrugs of high stability in plasma and liver homogenate. The use of the lactate ester linker gave prodrugs of high stability in plasma with slow hydrolysis in liver homogenate; such conjugates may have potential in controlled release systems or as prodrugs for drug targeting. In contrast, using diethylene glycol as a linker yielded an ester conjugate that showed high chemical stability, but readily released drug in plasma and liver homogenate. Cytotoxicity studies indicated non-toxic effects of G0 dendrimer and conjugates on Caco-2 monolayers. Conjugation of naproxen toG0PAMAMdendrimer appreciably increased its permeability in both directions. Amore pronounced increase of naproxen transport was observed when a lauroyl chain was attached to the surface of G0 PAMAM dendrimers. Results suggest that G0 PAMAM dendrimers demonstrate potential as nanocarriers for the enhancement of oral bioavailability [51].

Dendrimers for Transdermal Delivery: Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. Stratum corneum acts as a major barrier for most of the drugs. PAMAM dendrimer complex with drugs could be improving the drug permeation through the skin as penetration enhancers. Chauhan AS and *et al.,* investigated PAMAM dendrimers enhances the bioavailability of indomethacin in transdermal delivery applications. The effect of three different PAMAM dendrimers on the aqueous solubility of indomethacin and the bioavailability improvement was investigated. G4.0-NH_2, G4.0-OH, and G4.5 PAMAM dendrimers were

used and the order of solubility enhancement of indomethacin as G4.0-NH_2 > G4.0- OH > G4.5. It was noticed that with amine terminated dendrimers the solubility was enhanced on the basis of electrostatic interactions between the carboxyl group of indomethacin and the amino groups of the dendrimer. In case of G4.5 PAMAM and G4-OH PAMAM the proposed mechanism was molecular encapsulation and hydrogen bonding, respectively.

From this study with dendritic polymers, it could be concluded that the proposed system displayed better drug- targeting efficiency to the arthritic regions with sustained drug delivery [52]. Cheng Y *et al.,* studied the model drugs Ketoprofen and Diflunisal. These were conjugated with G5 PAMAM dendrimer and investigated for different studies. In vitro permeation studies on excised rat skin showed 3.4 times higher permeation of Ketoprofen from Ketoprofen–dendrimer complex than that from 2mg/mL Ketoprofen suspended in normal saline. Similarly, a 3.2 times higher permeated amount was observed with Diflunisal–dendrimer complex. Anti-nociception effect of drugs was studied on mice, results showed that Ketoprofen–dendrimer complex reducing writhing activity during the period of 1–8 h after Transdermal administration, while pure Ketoprofen suspension at the equivalent dose of Ketoprofen significantly decreased number of writhing between 4 and 6 h [53].

Wang *et al.,* synthesized polyhydroxyalkanoate (PHA) matrix restraining PAMAM dendrimers penetrated quantity of tamsulosin through snake skin was 15.7 $\mu g/cm^2$ /d and 24$\mu g/cm^2$ /d from PHA and PAMAM dendrimers containing PHA matrices, correspondingly. It is found that PAMAM dendrimers enhances the diffusion of tamsulosin. They concluded that the PAMAM dendrimers itself does not voyage in the interior of the skin; however, it takes steps as polymeric skin permeation enhancer by altering the macroscopic constitution of water in the solution [48, 54].

Dendrimers for Pulmonary Delivery: Pegylated dendrimeric micelles prolong the half-life of low molecular weight heparin (LMWH), Enoxaparin and increase the drug's pulmonary absorption, thereby efficacious in preventing deep vein thrombosis (DVT) in a rodent model. Shuhua Bai have prepared dendrimers of LMWH entrapped in PEG these produced a significant increase in pulmonary absorption and the relative bioavailability of the formulation was 60.6% compared to subcutaneous LMWH. The half-life of the PEG–dendrimer-based formulation was 11.9 h, which is 2.4-fold greater than the half-life of LMWH in a saline control formulation. When the formulation was administered at 48-h intervals, the efficacy of LMWH encapsulated in pegylated dendrimers in reducing thrombus weight in a rodent model was very similar to that of subcutaneous LMWH administered at 24-h intervals [55].

Dendrimers for Targeted Delivery: Dendrimers have ideal properties which are useful in targeted drug-delivery system. The targeted delivery of chemotherapeutics to tumor cells reduced side effects compared to systemic delivery. Macromolecular delivery of anti-cancer drugs using multifunctional dendritic architectures allows for the conjugation of both drugs and targeting moieties such as folic acid, monoclonal antibodies, and peptides to the dendrimer periphery for increasingly specific delivery. The two general strategies of targeting include the passive targeting of bulk cancerous tissue and the active targeting of unique tumor cells.

Non-specific or passive targeting of tumors is achieved by increasing the hydrodynamic radius of the dendrimer though Pegylation, leading to the accumulation of dendrimer in tumor tissue via the enhanced permeability retention (EPR) effect. The EPR effect is a result of tumor induced angiogenesis leading to neovasculature that is irregular, leaky or defective with disorganized endothelial cells; tumor tissues also suffer from poor lymphatic drainage, all leading to the accumulation and retention of macromolecules in the

tumor mass Specific or active targeting relies on the conjugation of one or more targeting moieties to the dendrimer to facilitate cell-receptor-mediated interactions [56].

Hong *et al*., explicitly quantified the binding avidity of multi-valent targeted G5-PAMAM containing different numbers of folic acid molecules Binding avidity to folic acid receptor-over expressing cells increased with each additionally bound FA molecule conjugated to the dendrimer, saturating at 5-6 moieties per dendrimer, though the rate of intracellular internalization was not significantly affected with increased binding. The dendrimers demonstrated a dramatic enhancement of binding avidity of almost 5 orders of magnitude. It was suggested that aggregates of 5-6 FA receptors are pre organized on the membrane and that the key factor in reported tumor reduction is enhanced residence time on the cell and not the rate of endocytosis [57].

Methotrexate can be successfully targeted by using folic acid. The Baker group has investigated several variations of folic acid-conjugated dendrimers for targeted drug delivery. Surface conjugated folic acid G5-PAMAM dendrimers were prepared where the remaining free amine groups were capped with glycidol to neutralize the positive charges, and then further reacted with methotrexate (MTX) to form ester linkages A comparison between encapsulated MTX vs. covalently bound drug release showed a rapid release for the free drug over 2.5 h (~75%), compared to a much slower release for the bound drug over the same period of time (~5%).

Furthermore, encapsulated drug displayed diffusion characteristics similar to free drug. Folic acid-targeted MTX conjugates demonstrated high specificity for KB cells over expressing folic acid receptors [58]. In a separate study, folic acid, fluorescein, and methotrexate were conjugated to PAMAM and examined in vitro against KB cells. Anti-proliferative activity was slightly lower for the dendrimer-drug conjugates compared to free methotrexate. Dose-dependent binding to KB cells was demonstrated and compared to fluorescein-modified PAMAM not containing folic acid. Targeting was diminished yet still significant against KB cells under expressing FA receptors. The drug-dendrimer conjugates became ineffective when the cells were pretreated with free folic acid. A comparable study was performed with folic acid, fluorescein, and paclitaxel conjugated to partially acetylated PAMAM dendrimers. Again, folic acid-targeting occurred, preferentially delivering paclitaxel-conjugated dendrimers to KB cells. Internalization was not detected when dendrimers were exposed to down-regulated KB cells [26, 59, 60].

Dendrimers for Bacterial and Viral Infection: Sialylated dendrimers, called sialo dendrimers, have been used to treat influenza infection. The first step in the infection of a cell by influenza virus is the attachment of the virion to the cell membrane. The attachment occurs through the interaction of a virus receptor haemagglutinin with sialic acid groups presented on the surface of the cell [61]. Sialodendrimers bind to haemagglutinin and thus prevent the attachment of the virus to cells. Attaching sialinic acid moieties to the dendrimer surface enhances the therapeutic effect and allows the dendrimer to attain a higher activity in inhibiting influenza infection. A larger effect occurs with an increase in the number of sialinic acid groups [62, 63].

Poly (lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs). This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities [64, 65]. The general mode of action of antibacterial dendrimers is to adhere to and damage the anionic bacterial membrane, causing bacterial lysis.[66] PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be

potent antibacterial biocides against Gram positive and Gram negative bacteria. The nature of the counter ion is important, as tetra-alkyl ammonium bromides were found to be more potent antibacterials over the corresponding chlorides [67]. Poly (lysine) dendrimers with mannosyl surface groups are effective inhibitors of the adhesion of E. coli to horse blood cells in a haemagglutination assay, making these structures promising antibacterial agents [68]. Triazine-based antibiotics were loaded into dendrimers beads at high yields. The release of the antibiotic compounds from a single bead was sufficient to give a clear inhibition effect [69].

Michelle K. Calabretta *et al*., investigated amino-terminated G5 PAMAM dendrimers are effective antimicrobial agents against common Gram-negative and Gram-positive pathogens *P. aeruginosa* and *Staphylococcus aureus.* Although unmodified, amino-terminated PAMAM is toxic to Human Corneal Epithelial Cells, partial coating of the dendrimers with PEG reduces cytotoxicity. The partial PEG coating maintains a high toxicity to the Gram-negative pseudomonal species, although it results in a large decrease in toxicity to Gram-positive staphylococcal species. These findings show that PAMAM derivatives could be an excellent candidate for a new class of antimicrobial compounds that could be incorporated to contact lenses to combat pseudomonal keratitis [70].

Dendrimers in Gene Transfection: Dendrimers can act as vectors, in gene therapy. Amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus [71, 72]. 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 due to their enhanced flexibility, which allows the formation of more compact complexes with DNA. It has been found that maximum transfection efficiency is obtained with a net positive charge on the complexes (i.e., an excess of primary amines over DNA phosphates) [73, 74, 75]. Kukowska-Latallo et al. reported that intravenous administration of G9 PAMAM dendrimer-complexed pCF1CAT plasmid could result in high level of gene expression in the lung tissues of rats. It enhances the transfection efficiency and expression pattern of dendrimers [76].

Other Applications:

Dendrimers as Imaging Agent: Paramagnetic metal chelates such as Gd(III)-N, NV, NW, Nj-tetracarboxymethyl-1, 4, 7, 10-tetraazacyclododecane (Gd (III)-DOTA), Gd(III)-diethylenetriamine pentaacetic acid (Gd(III)-DTPA), and their derivatives increase the relaxation rate of surrounding water protons and are used as contrast agents for magnetic resonance imaging (MRI) However, shortcomings of these low molecular weight contrast agents are short circulation times within the body and inefficient discrimination between diseased and normal tissues.

Lauterbur, Wiener and Tomalia pioneered the use of dendrimer-based MRI contrast agents by reporting some of the highest known relaxivities for these agents [77, 78]. These extraordinary properties have been studied extensively in vivo during the last decade by Kobayashi and Brechbiel. These properties appear to result from a combination of the geometrical amplification of chelated gadolinium that is possible on a dendrimers surface and higher rotational correlation times with minimal segmental motion that are intrinsic to these dendrimer conjugates. Consequently, dendrimer-based Gd(III) chelates consisting of generations 2 and 6 PAMAM dendrimers with 12 and 192 terminal surface amines conjugated to the chelating ligand 2-(4-isothiocyanatobenzyl)-6-methyl diethylene triamine pentaacetic acid through a thiourea linkage were synthesized and used *in vivo* with rabbits. These contrast agents exhibited excellent MRI images of blood vessels upon intravenous injection. The blood circulation times were sufficiently long, with more than 100 min for large dendrimer conjugates such as the G = 6 PAMAM-TU-Gd(III) - DTPA [79, 80].

Boron Neutron Capture Therapy: Boron neutron capture therapy is a cancer treatment based on a nuclear capture reaction. When 10B is irradiated with low energy or thermal neutrons, highly energetic a-particles and 7Li ions are produced that are toxic to tumor cells. To achieve the desired effects, it is necessary to deliver 10B to tumor cells at a concentration of at least 109 atoms per cell. One study, involving intratumoral injection of a conjugate between PAMAM dendrimer G5 carrying 1100 boron atoms at its surface and cetuximab, the monoclonal antibody specific for the EGF receptor, showed that the conjugate was present at an almost 10-fold higher concentration in brain tumors than in normal brain tissue [81].

Tissue Engineering (Te) Applications of Dendrimers: The use of dendrimers' architectures in cells and TE applications is still in its infancy. Ligand-modified dendrimers have been proposed for use as substratum for cell culture and high performance bioartificial organs [82]. Dendrimers are used in bone, cartilage tissue engineering.

CONCLUSION: The main purpose of this review is to focus various valuable applications of dendrimers which can be platform for the development of optimized novel drug delivery systems. Dendrimers drug delivery is in its infancy, it offers several attractive features. This novel class of polymers and their derivatives exhibit unique physicochemical and biological properties, which have great potential for use in a variety of applications. It has greater flexibility in design.

High control over the branching length, shape and size allows modification according to delivery system, so these can serve as ideal carrier for drug and various other applications. We still do not know whether these synthetic polymers, once they entered the body can cause damage to other tissues. Even though toxicity problems if arise, they will be minimized by modifying dendrimer architecture. As the synthesis involves multistep process future work is necessary to find out cost effective synthesis strategies with minimum efforts and the relationship between dendrimer-drug molecules for effective commercial utilization of this technology.

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