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Rajesh Akki

Department of Pharmaceutics,
Hindu College of Pharmacy,
Guntur, Andhra Pradesh, India

Munagala Gayatri Ramya

University college of
Pharmaceutical Sciences,
Acharya Nagarjuna University,
Nagarjuna Nagar, Guntur,
Andhra Pradesh, India

Ch Sadhika

Department of Pharmaceutics,
Hindu College of Pharmacy,
Guntur, Andhra Pradesh, India

D Spandana satya

Department of Pharmaceutics,
Hindu College of Pharmacy,
Guntur, Andhra Pradesh, India

Correspondence

Rajesh Akki

Department of Pharmaceutics,
Hindu College of Pharmacy,
Guntur, Andhra Pradesh, India

A novel approach in drug delivery system using dendrimers

Rajesh Akki, Munagala Gayatri Ramya, Ch Sadhika and D Spandana Satya

Abstract

Dendrimers are novel synthetic polymeric systems having improved physical and chemical properties due to their unique three dimensional architecture. Due to their unique characteristics, dendrimers have attracted a great deal of attention over the past few years. The reason why they are of eminent interest in drug-delivery applications is that they have uniform size, water solubility, modifiable surface functionality and available internal cavities. Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behaviour dendrimers are suitable for a wide range of biomedical and industrial applications. The paper gives a concise review of dendrimers' physico-chemical properties and their possible use in various areas of research, technology and treatment.

Keywords: novel approach, drug delivery, dendrimers

Introduction

Arthritis is an autoimmune disease and disorder of the joints characterized by inflammation of one or more joints of the body part ^[1, 2]. The use of NSAID's is ubiquitous in the management of arthritic condition due to their effectiveness as anti-inflammatory and analgesic activity ^[3]. Meloxicam (MLX) is a oxicam derivative, is a member of the enolic acid group of NSAID's. MLX has been effectively used in symptomatic management of the rheumatoid arthritis and osteoarthritis. MLX have lower toxicity than the other NSAIDs with similar efficacy for reducing the pain and anti-inflammatory symptoms. NSAIDs including MLX is characterized by their gastrointestinal adverse effects which include ulceration, bleeding, inflammation and perforation of the stomach. So oral route is not obvious route for the administration of MLX. Considering all these issues it's become mandatory to develop other drug delivery system other than oral to overcome the problems associated with current delivery technology. Dendrimers are potential permeation enhancer as well as solubility enhancer ^[4, 5]. The therapeutic efficacy of a drug in an appropriate dose might decrease due to its inadequate access to the target site of action in the body. To overcome this problem, drug is usually given high doses to the body to show the desired impact. Disappearance of the remedial effectiveness of drug substances stems from the low solubility of drug pharmaceutical ingredients in the aqueous environment of the human body. Results of the studies conducted in medicinal chemistry have shown that water-soluble derivatives of the chemical formulations of drugs can be prepared successfully; however, even small constructional changes in the structure may lead to the dramatic decreases in their efficacy ^[6]. Drug carriers are defined as any substances incorporating to improve the delivery and the effectiveness of drugs ^[7]. Various drug carrier systems such as liposomes, micelles, nanoparticles, and nanorods are used to perform the desired release of the drugs having weak solubility and therefore, low bioavailability in the body, and to minimize the interaction of the drugs with the healthy tissues ^[8]. Regarding these systems, the main encountered drawbacks are instability within the body, interaction with the healthy tissues, allowing absorption in the kidneys due to nano sizes, and thus, expelling out the blood circulation ^[9, 10]. To avoid these handicaps, dendrimers can take over as potential drug delivery systems ^[11].

Dendrimers are highly branched polymer of nano size. These are three dimensional, monodisperse, globular macromolecules having high number of functional groups on their surface. Dendrimers are synthesized by series of repetitive steps. The idea of repetitive growth with branching was first reported by Vogtle ^[12].

This was followed by independent development of the divergent, macromolecular synthesis of “true dendrimers” by Tomalia [13, 14]. The first synthesized dendrimers were polyamidoamines (PAMAM). They are also known as starburst dendrimers. The term starburst is a trademark of the Dow chemicals company. Ammonia was used as the core molecule. The term originates from “Dendron” meaning a tree in Greek. At the same time Newkome group independently reported synthesis of similar macromolecules [15]. They called ‘arborols’ (from latin word ‘arbor’) also meaning a tree.

Dendrimers are highly branched polymers which have special characteristics like different functional end groups, higher density and lesser viscosity [16- 19]. Due to these unique features this class of polymeric nanomaterial have various applications in different fields like as drug delivery [20- 24], dendrimer based nanomedicine [25], gene delivery [26], light harvesting [27], dendritic nanomaterials [28], electrode design [29], solubility enhancers [30] and for various biotech

applications [31]. A typical dendrimer is comprised of three different topological parts: (a) a central core which is either a single atom or an atomic group having at least two identical chemical functions; (b) building blocks with several interior layers composed of repeating units; and (c) multiple peripheral functional groups, generally located on the exterior of the macromolecule, which play a key role in their properties. The first part, the focal core, encapsulates various chemical species that exhibit unparalleled properties due to the special nanoenvironment surrounded by extensive dendritic branching. Next, the various interior layers composed of repeating units provide a flexible space created within the voids of dendritic building blocks, which are able to encapsulate various small guest molecules. Finally, the third part of a dendrimer is the multivalent surface, which can accommodate a large number of functionalities which can interact with the external environment, there by defining the dendrimer’s macroscopic properties [32].

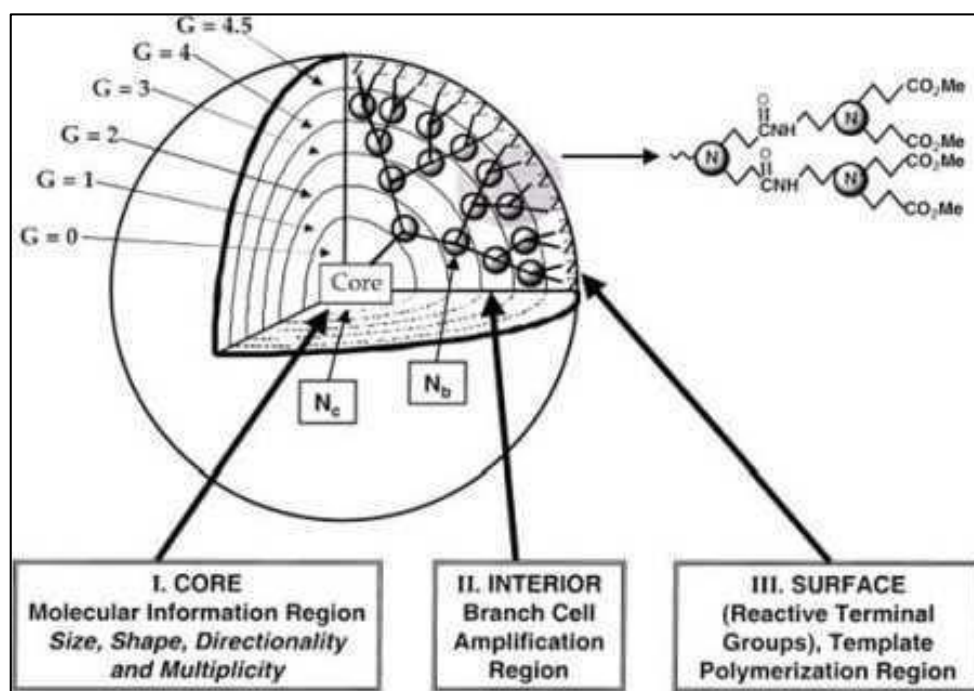


Fig 1: Three-dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface

Table 1: Types of dendrimers and discovered by

S. No	Type of Dendrimer	Discovered by
1.	Polyamidoamine (PAMAM) Dendrimer	Tomalia
2.	Arborols	Newkome (Newkome <i>et al.</i> , 1985) [15]
3.	Polypropyleneimine (PPI) Dendrimer	De Brabander and Meijer
4.	Polyether dendrimer	Frechet (Grayson and Frechet, 2001) [21]

Synthesis of dendrimers

Dendrimers are assembled from multifunctional core which is extended outward by a series of reactions called Michael addition reactions [33]. Each step of the reaction must be driven to conclusion in order to prevent trailing generations (some branches becoming shorter than others). The presence of trailing generations (impurities) can create negative impacts on the symmetry and functionality of the dendrimer, besides dendrimers are very difficult to purify because the relative size difference between perfect and imperfect dendrimers is diminutive. It is also a known fact that synthetic procedure can be applied to manage the size and number of

branches on a dendrimer. There are two established methods for dendrimer synthesis, divergent and convergent synthesis, the choice of method for synthesis depends greatly on the target end application.

1. Divergent synthesis

The divergent approach arose from the seminal work of Tomalia [35] and Newkome *et al.* [36] in the early 1980s [34]. The divergent approach to dendrimer synthesis is based on the construction of a molecular superstructure starting with a focal point or core and progressing outward to the periphery. This approach involved assembling monomeric modules in a

radial, branch-upon-branch motif according to certain dendritic rules and principles [37, 38]. The basic operations consist of coupling step and activation step. Coupling step introduces a new latent branch point at each coupling site by the reaction of the peripheral functionalities of the core with the complementary reactive group of the monomer and activation step activates end-functionalities of the periphery to create new reactive surface functionalities [34, 39]. As the number of generations of dendrimers continues to increase, the number of surface functionalities also increases exponentially. That is to say, assuming that the monomer's functional group (s), steric hindrance and active site accessibility do not interfere with the construction of ideal dendrimers, the divergent process permits the exponential growth of free active sites per generation. Therefore, in order to obtain high generation dendrimers, excess monomer loading and lengthy chromatographic separations are required, a feat that can be quite difficult to achieve, even with highly efficient reactions [34, 38].

2. Convergent synthesis

The convergent method developed by Frechet, uses top-down approach in which the synthesis starts from the periphery and ends towards the central core. 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 steric problems occur in the reactions of the dendrons and the core molecule [40]. 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. The main advantage of this approach is the ability to precisely control the molecular weight and produce dendrimers having functional groups at the accurate and exact position. Moreover, inactive products can easily be removed by purification after each generation of dendrimer. Hence, products are more standardized although the purification of higher generation dendrons may become difficult as a consequence of increasing resemblance between the reactants and the formed products. Therefore, convergent growth approaches are generally restricted to the creation of lower generation dendrimers because of nanoscale steric problems arising when conferring the dendrons to the core [41]. The synthesis of poly (aryl ether) dendrimers is one common example of this method (Grayson, Frechet, 2001) [21]. The advantages of convergent methodology include easy purification of the desired product, defect minimized final product, easy and precise placement of peripheral functional groups.

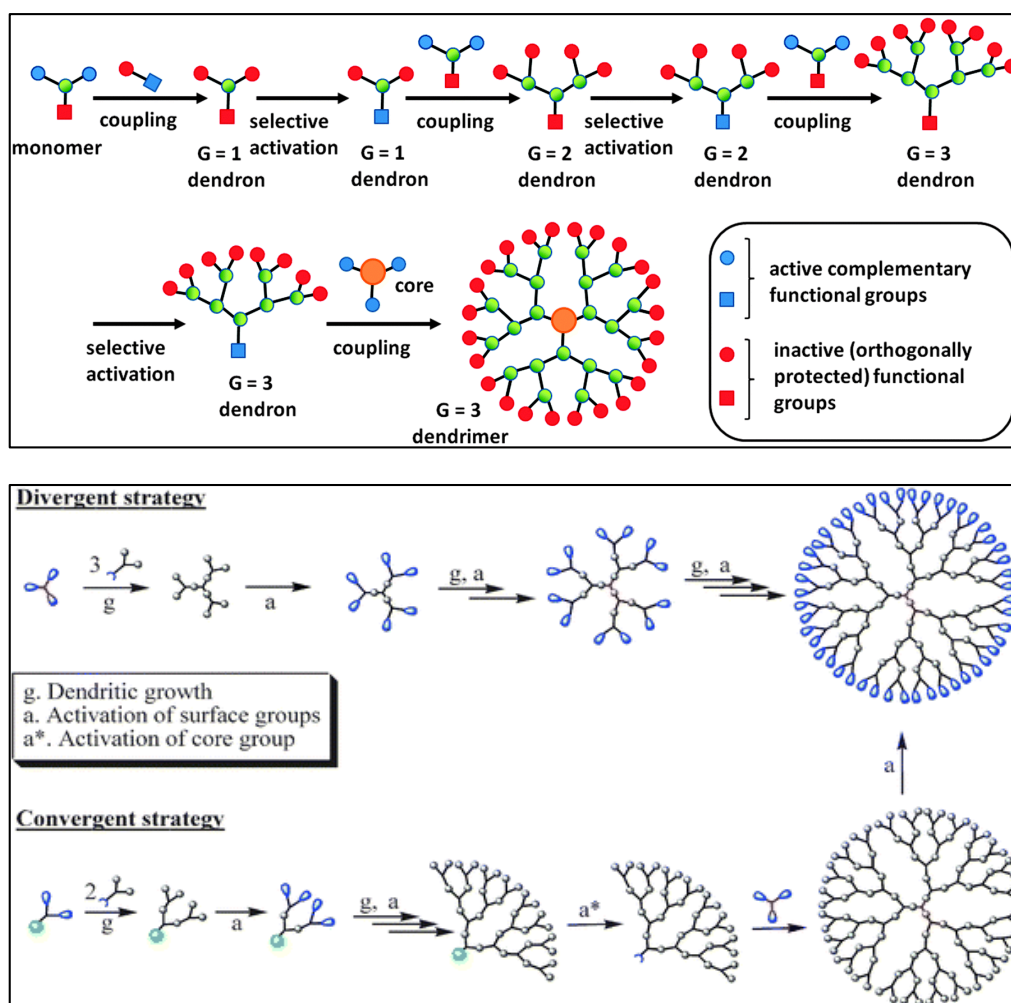


Fig 2: Synthesis of dendrimers in both convergent and divergent synthesis

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.

Advantages

- Improves the solubility of poorly soluble drug
- Increases the stability of active ingredient within the cores.
- Uniform in size enhance their stability to cross membrane and also reduce the undesired clearance from the body.
- Presence of dynamic internal cavities where ions or internal molecules can be hosted.
- Targeted delivery is possible via targeting ligand conjugated to the dendrimer surface.

Properties of dendrimers

Dendrimers are nanoscale sized that have similar dimensions to important bio-building blocks like proteins, DNA. Multiple numbers of terminal surface groups (Z) enables bio-conjugation of drugs, signalling groups, targeting moieties or biocompatibility groups. The dendrimer surfaces may be designed with functional groups to augment or resist trans-cellular, epithelial or vascular bio permeability. The 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. Non-or low immunogenicity associated with most dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG). Surface groups can be modified to optimize biodistribution; receptor mediated targeting, therapy dosage or controlled release of drug from the interior space. Dendrimers have ability to be excreted from body as a function of nanoscale diameter. Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different size, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis^[42]. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solution has 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 behaviour is unlike that of linear polymers.

For classical polymers the intrinsic viscosity increases continuously with molecular mass. The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Dendrimers solubility is strongly influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. A marked difference was also observed in chemical reactivity. Dendritic polyesters were debenzylated by catalytic hydrogenolysis whereas linear polyester was unreactive. Dendrimers have some unique properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior^[43, 44]. The spherical shape of dendritic molecule has important implications for its rheological properties both in bulk and in solution. The interaction of spherical molecules with solvent molecules is different from that of linear molecules^[45]. Dendrimers are monodisperse macromolecules, unlike linear polymers. The classical polymerization process which results in linear polymers is usually random in nature and produces molecules of different sizes, whereas size and molecular mass of dendrimers can be specifically controlled during synthesis. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Dendrimer solutions have significantly lower viscosity than linear polymers^[46]. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline^[47]. Such behaviour is unlike that of linear polymers. For classical polymers the intrinsic viscosity increases continuously with molecular mass. The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Dendrimers' solubility is strongly influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in nonpolar solvents. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester. A marked difference was also observed in chemical reactivity. Dendritic polyester was debenzylated by catalytic hydrogenolysis whereas linear polyester was unreactive. Lower generation dendrimers which are large enough to be spherical but do not form a tightly packed surface, have enormous surface areas in relation to volume (up to 1000 m²/g) (48). Meijer and co-workers^[14, 15] trapped small molecules like rose bengal or p-nitrobenzoic acid inside the 'dendritic box' of poly(propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting the terminal amines with an amino acid (L-phenylalanine) and guest molecules were stably encapsulated inside the box.^[49, 50] Hydrolysing the outer shell could liberate the guest molecules. The shape of the guest and the architecture of the box and its cavities determine the number of guest molecules that can be entrapped. Meijer's group described experiments in which they had trapped four molecules of rose Bengal or eight to ten molecules of p-nitrobenzoic acid in one dendrimer. Archut and co-workers^[51] developed a method in which boxes could be opened photochemically. A fourth

generation polypropylene imine dendrimer with 32 end groups was terminated in azobenzene groups. The azobenzene groups undergo a fully reversible photoisomerization reaction. The E isomer is switched to the Z form by 313 nm light and can be converted back to the E form by irradiation with 254 nm light or by heating. Such dendrimers can play the role of photo switchable hosts for eosin Y. Photochemical modifications of the dendritic surface cause encapsulation and release of guest molecules. Archut's experiment demonstrated that the Z forms of the fourth generation dendrimers are better hosts than the E forms. It is possible to create dendrimers which can act as extremely efficient light-harvesting antennae [52, 53]. Absorbing dyes are placed at the periphery of the dendrimer and transfer the energy of light to another chromophore located in the core. The absorption spectrum of the whole macromolecule is particularly broad because the peripheral chromophores cover a wide wavelength range. The energy transfer process converts this broad absorption into the narrow emission of the central dye. The light harvesting ability increases with generation due to the increase in the number of peripheral chromophores. Biological properties of dendrimers are crucial because of the growing interest in using them in biomedical applications. "Cationic" dendrimers (e.g., amine terminated PAMAM and poly (propylene imine) dendrimers that form cationic groups at low pH) are generally haemolytic and cytotoxic. Their toxicity is generation-dependent and increases with the number of surface groups [54].

Applications

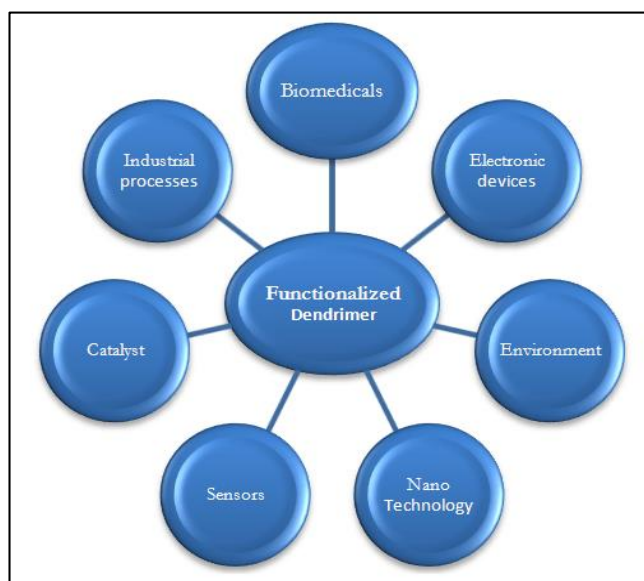


Fig 3: Applications of dendrimers

Pharmaceutical applications

- 1. Dendrimers in pulmonary drug delivery:** Dendrimers have been reported for pulmonary drug delivery of Enoxaparin by 40% G2 and G3 generation positively charged PAMAM dendrimers were reported to increase the relative bioavailability of Enoxaparin. The positively charged dendrimer, which was effective in deep vein thrombosis forms complex with enoxaparin after pulmonary administration [55].
- 2. Dendrimer in transdermal drug delivery:** Dendrimers has been found to improve solubility and plasma

circulation time via transdermal formulations and to deliver drugs efficiently. To improve the drug permeation through the skin as penetration enhancers PAMAM dendrimer complex with NSAIDs have been reported. 3.4 and 3.2 times higher permeation has been shown when Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer. Enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application was reported to be effective [56-58].

- 3. Dendrimer in oral drug delivery:** Oral drug delivery studies using the human colon adenocarcinoma cell line, CaCo2, have indicated that low generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the P-glycoprotein efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. DNA assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents [59, 60].
- 4. Dendrimer hydrogel for ocular drug delivery:** Dendrimers are especially ideal for synthesizing hydrogels, cross-linked networks that increase in volume in aqueous solution 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. By synthesizing a hydrogel composed of PEGylated dendrimers that contain ocular drug molecules attached to the dendrimers efficiently deliver the drugs to the eye [61].
- 5. Dendrimers for controlled release drug delivery:** The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construct involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5 fluorouracil. Encapsulation of 5-fluorouracil into G4 increases in the cytotoxicity and permeation of dendrimers. The earlier discussed dendrimer drug interaction techniques are used to control the drug delivery. A third-generation dendritic unimolecular micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control. Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers [62-65].
- 6. Dendrimers in targeted drug delivery:** Dendrimers have ideal properties which are brought in application in targeted drug delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains possessed reasonable drug loading, a reduced release rate and

reduced haemolytic toxicity compared with the non-PEGylated dendrimer [69-71]. The star polymer were reported to give the most promising results regarding cytotoxicity and systemic circulatory half-life (72 hrs). In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumours. Combined these factors lead to the selective accumulation of macromolecules in tumour tissue, a phenomenon termed the 'Enhanced Permeation and Retention' (EPR) effect. Therefore, the anticancer drug doxorubicin was reported to be covalently bound to this carrier via an acid-labile hydrazone linkage. The cytotoxicity of doxorubicin was significantly reduced (80–98%), and the drug was successfully taken up by several cancer cell lines [66-68].

7. Dendrimers as anticancer drug carriers: Initial studies of dendrimers as potential delivery systems focused on their use as unimolecular micelles and “dendritic boxes” for the noncovalent encapsulation of drug molecules. For example in early studies, DNA was complexed with Pamam Dendrimers for gene applications [72], and hydrophobic drugs and dye molecules were incorporated in various dendrimer cores [73-76]. An advantage of using dendritic unimolecular micelles rather than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected. However this approach suffers from a general drawback in that it is difficult to control the release of molecules from the dendrimer core. In some cases, harsh conditions are required, whereas in others the encapsulated is not well retained and molecules are released rapidly [77, 78]. PAMAM dendrimers gave conjugates that exhibited slower release, higher accumulation in solid tumours, and lower toxicity compared to free cisplatin [79].

8. Sensors: The unique structures and properties of dendrimers evolved interest in interfacing nanoscale dendrimers in the sensing of chemical and biological species. It is on record that various nanoparticles are used in the development of miniaturized, rapid, ultrasensitive and inexpensive environmental monitoring devices. Touzani reported that a Poly (Amidoamine) dendrimer with 1,8- Naphthalinamide surface groups is capable of acting as a Photo induced Electron Transfer (FET) fluorescent sensor for rare earth metals and metal cations, his investigation showed that the presence of metal ions evolves a Photo induced Electron Transfer (PET) leading to an enhancement in the fluorescence [80].

9. Therapeutic activity of dendrimers: Dendrimers are being evolved as topical antimicrobial agents following exploration of effectiveness of polylysine dendrimers against herpes simplex virus (HSV), currently under Phase II clinical trials for its efficacy against vaginal infection. SPL7013 Gel (Viva Gel®) developed by Starpharma Pty Ltd (Melbourne, Australia) is a vaginal microbicide for the prevention of HIV and HSV infections [81]. The active ingredient of this Carbopol-based aqueous gel is a dendrimer comprising a divalent benzhydrylamine (BHA) core, four generations of lysine branches with the outermost branches capped with a total

of 32 naphthalene disulfonic acid groups that impart hydrophobicity, and a high anionic charge to the dendrimer surface [82]. Success of VivaGel® (Starpharma) gave a philip to the other possible applications of dendrimers. Wang *et al.* assessed mechanism of antimicrobial activity of PAMAM dendrimers in guinea pig model of chorioamnionitis against *E. coli* induced ascending uterine infection. The authors attributed the antimicrobial activity to the interaction of polycationic dendrimers with polyanionic lipopolysaccharide present in *E. coli* [83]. Later it was observed that 3.5G PAMAM dendrimers glycosylated with glucosamine exhibited anti-inflammatory activity by inhibiting complex of lipopolysaccharide, Toll-like receptor 4 (TLR4) and MD-2, which mediates the proinflammatory cytokine responses [84]. This activity of partially glycosylated dendrimers could provide a platform for exploration of dendrimers in the treatment of malignancies, inflammatory diseases as well as infectious diseases.

10. Reduction of toxicity: Although dendrimers with cationic surface groups cause cytotoxicity and hemolytic toxicity yet their toxicity can be alleviated by modification of surface groups with biocompatible ligands such as PEG, acetyl group, carbohydrates, amino acids and peptides etc. The surface engineering of dendrimers results in biocompatible dendrimers as well as reduces the toxicity of some cytotoxic and hemolytic bioactives [85, 88]. Dendrimers show the surface charge-, concentration- and generation-dependent cytotoxicity. The permeability profile of dendrimers is also related to its surface charge. Cationic dendrimers have been found to be more toxic (hemolytic as well as cytotoxic) and more permeable than the anionic and neutral dendrimers. Designing of biocompatible and biodegradable dendrimers either by synthesizing dendrimers from biocompatible units (peptides, amino acids, carbohydrates etc.), or modifying the surface of cationic dendrimers with biocompatible ligands (PEGylation, acetylation, glycosylation etc.), will facilitate reduction in toxicity [86, 87].

11. 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 [89]. The ideal vector for transfection should have high efficiency, non-immunogenic, non-toxic, either biodegradable 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 Super Fect™ consisting of activated dendrimers is commercially available. These activated dendrimers can carry a larger amount of genetic material than viruses. Super Fect–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^[90].

Conclusion

In this paper the application of dendrimer in pulmonary drug delivery system, oral drug delivery system, controlled and targeted drug delivery system in gene transfection, in reduction of toxicity, in anticancer property and etc. The characteristics of dendrimers, including high branching, well-defined globular structures, excellent structural uniformity, multivalency, variable chemical composition, and high biological compatibility, makes these compounds ideal carriers in biomedical applications such as drug delivery, imaging, and tissue engineering. Dendrimers are an important tool for drug discovery because of their ease of surface modification as well as their ability to interact with charged functional groups. On the other hand, dendrimers in the design of electrochemical detectors are promising research field for the development of new tools for supporting the diagnosis of diseases in a short time without a pretreatment of sample obtaining the lowest DL and QL in vivo detecting.

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