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# Dendrimers: As a potential carrier for medicaments

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## Abstract

The objective of nanomedicine is to control and manipulate biomacromolecular constructs and supramolecular assemblies that are critical to living cells in order to improve the quality of human health. So, nanostructured carrier was developed which have high level of control possible over the architectural design of dendrimers; their size, shape, branching length/density, and their surface functionality, clearly distinguishes these structures as unique and optimum carriers in those applications. Dendrimers are currently attracting the interest of a great number of scientists because of their unusual chemical and physical properties and the wide range of potential application in such different fields as medicine, biology, chemistry, physics and engineering.

**Key words:** Dendrimers, Structure, Synthesis, Characterization, Application.

## Introduction

Every year approximately $65 billion in drug revenues is accounted for by active pharmaceutical ingredients (APIs) with suboptimal bioavailability. The oral drug delivery market with $35 billion is the largest industry segment and is expected to grow as much as ten percent per year. The pulmonary drug delivery market reached $25 billion in 2006 with expected high steady growth in the next five years, and the implantable/injectable delivery market is expected to grow from about $5 billion to over $12 billion by 2010. About forty percent of newly developed APIs are rejected by the pharmaceutical industry and will never benefit a patient because of poor bioavailability due to low water solubility and/or cell membrane permeability. In addition, about seventeen percent of launched APIs exhibit suboptimal performance for the same reasons. Giving the growing impact and need for drug delivery, a thorough understanding of delivery technologies that enhance the bioavailability of APIs is of high importance.

So, 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. The high level of control over the dendritic architecture (size, branching density, surface functionality) makes dendrimers ideal carriers in these applications.

Dendrimers, a nanoparticle-based drug-delivery system have numerous applications in pharmaceuticals such as enhancing the solubility of poorly soluble drugs, enhancing the delivery of DNA and oligonucleotides, targeting drug at specific receptor site, and ability to act as carriers for the development of drug delivery systems[1].

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Dendrimers are complex but well defined multi-branched chemical compounds, with a high degree of order, and the possibility of containing selected chemical units in predetermined sites of their tree-like structure[2,3]. Dendrimer chemistry is a rapidly expanding field for both basic and applicative reasons . From a topological viewpoint, dendrimers contain three different regions: core, branches, and surface. Another important property of dendrimers is the presence of internal cavities where ions or neutral molecules can be hosted . Such a property can potentially be exploited for a variety of purposes, which include catalysis and drug delivery.

Dendrimers are globular, nano-scaled macromolecules with a particular architecture constituted of three distinct domains: (i) a central core which is either a single atom or an atomic group having at least two identical chemical functions, (ii) branches emanating from the core, constituted of repeat units having at least one branch junction, whose repetition is organized in a geometrical progression that results in a series of radially concentric layers called generations, and (iii) many terminal functional groups, generally located in the exterior of the macromolecule, which play a key role in the properties. With the emergence of a large number of applications in various fields, there is a critical need for techniques of characterization of dendrimers, but this task is not trivial due to their very peculiar structure. Indeed, not only their chemical composition but also their morphology, their shape and their homogeneity must be determined[4].

**Advantages of Dendrimers:**

1. Improve the solubility of poorly soluble drugs.
2. Increase the stability active ingredients within the cores.
3. Uniform in size to enhance their ability to cross the cell membrane and also reduce the undesired clearance from the body.
4. Presence of dynamic internal cavities where ions or neutral molecules can be hosted.
5. Targeted delivery is possible via targeting ligands conjugated to the dendrimer surface.
6. Many commercial small molecule drugs with anticancer, anti-inflammatory, and antimicrobial activity have been successfully associated with dendrimers.

**Structure of Dendrimer:**

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 size required by the investigator. The result is a spherical macromolecular structure whose size is similar to albumin and hemoglobin, but smaller than such multimers as the gigantic IgM antibody complex[5,6].

Dendrimers possess three distinguished architectural components, namely

(i) An initiator core.

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

(iii) Exterior (terminal functionality) attached to the outermost interior generations. (See figure 1.)

**Synthetic Approach of Dendrimers**

Synthesis approach of dendrimer were shown in Figure 2. Dendritic polymers or dendrimers are synthesized using a stepwise repetitive reaction sequence that guarantees a very highly monodisperse polymer, with a nearly perfect hyperbranched topology radiating from a central core and grown generation by generation[2]. The synthetic procedures developed for dendrimer preparation permit early complete control over the critical molecular design parameters such as size, shape, surface/interior chemistry, flexibility, and topology. (See figure 2.)

**Divergent Synthesis**

In the divergent approach, the dendrimer is prepared from the core as the starting point and built up generation by generation as shown in Figure 3. In the divergent way, problems occur from an incomplete reaction of the end groups, since these structure defects accumulate with the buildup of further generation. As the side products possess similar physical properties, chromatographic separation is not always possible. Therefore, the higher generations of divergently constructed dendrimers always contain certain structural defects. To prevent side reactions and to force reactions to completion, a large excess of reagents is required; however, this causes some difficulties in the purification of the final product. (See figure 3.)

**Convergent Synthesis**

The convergent approach starts from the surface and ends up at the core, where the dendrimer segments (dendrons) are coupled together as shown in Figure 4. In this way, only a small number of reactive sites are functionalized in each step, giving a small number of possible side-reactions per step. Therefore, each synthesized generation of dendrimers can be purified, although purification of high-generation dendrons becomes more cumbersome

because of increasing similarity between reactants and formed product. However,with proper purification after each step, dendrimers without defects can be obtained by the convergent approach. On the other side, the convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule. (See figure 4.)

## Characterization of Dendrimers:

### 1. Spectroscopy technique:

**A. Nuclear Magnetic Resonance (NMR) :** Nuclear Magnetic Resonance is most widely used for characterizing of dendrimers. NMR mainly used for analyzing step by step synthesis of dendrimer, to probe the size, morphology, dynamic of dendrimers, for organic dendrimers such ad PPI, polyphenylester[7-9].

**B. UV-Visible Spectroscopy :** UV–Visible spectroscopy can be used to monitor the synthesis of dendrimers, as shown for organoplatinum dendrimers in which a growth and decay of the metal to ligand charge transfer band is observed[10]. The intensity of the absorption band is essentially proportional to the number of chromophoric units, and can be a test for the purity of PPI dendrimers having azobenzene as end groups[11], for phosphorus dendrimers having azobenzenes with- in the branches[12], or double-layered carbosilane dendrimers[13].

**C. Infra-red (IR) and Raman Spectroscopy:** Infra-red spectroscopy is mainly used for the routine analysis of the chemical transformations occurring at the surface of dendrimers, such as the disappearance of nitrile groups in the synthesis of PPI dendrimers[14], the occurrence of hydrogen bonding in PPI glycine functionalized dendrimers[15], or the disappearance of the aldehydes during the synthesis of PMMH dendrimers[16].

**D. Fluorescence :** The high sensitivity of fluorescence has been used to quantify defects during the synthesis of dendrimers, such as unreacted $CO_2H$ groups in ARB dendrimer[17], but its main use is to characterize the structure of dendrimers having photochemical probes covalently linked to one particular section.

**E. X-ray diffraction :** This technique should allow precise determination of the chemical composition, size and shape of dendrimers.

**F. Mass spectrometry :** Classical mass spectrometry techniques such as chemical ionization or fast atom bombardment (FAB) can be used only for the characterization of small dendrimers, whos mass is b3000 D[18]. Electro-Spray Ionisation (ESI) can be used for dendrimers able to form stable multicharged species. It has been applied to PPI dendrimers[19], and to PAMAM dendrimers up to generation 10 [20].

### 2. Microscopy :

Transmission electron microscopy and Scanning electron microscopy are mainly used for imaging of dendrimers. Visualizing single molecules by optical microscopy has been successfully carried out for dendrimers having a fluorescent core. Confocal microscopy allowed to observe the fluorescence of a third generation PBzE dendrimer having a dihydropyrrolo pyrroledione as a core[21], and of polyphenylene dendrimers having peryleneimide as end groups[22].

### 3. Size exclusion chromatography (SEC):

Size Exclusion (or Gel Permeation) Chromatography allows the separation of molecules according to size. A detector such as a differential refractive index, or a LLS detector is connected to the SEC apparatus for the determination of the polydispersity, which is generally very close to unity. Most types of dendrimers were characterized by SEC, even self-assembled dendrimers[24].

### 4. Electrical techniques:

**A. Electron Paramagnetic Resonance:** Quantitative determination of the substitution efficiency on the surface of PANAM dendrimers[25].

**B. Electrochemistry:** It give information about the possibility of interaction of electroactive end groups.

**C. Electrophoresis:** Used for the assessment of purify and homogeneity of several type of water soluble dendrimers[25].

### 5. Rheology, physical properties :

**A. Intrinsic viscosity :** Rheology, and particularly dilute solution viscosimetry studies, can be used as analytical probe of the morphological structure of dendrimers.

**B. Differential Scanning Calorimetry (DSC) :** The DSC technique is generally used to detect the glass transition temperature (Tg), which depends on the molecular weight, entanglement and chain-end composition of polymers. The Tg is affected by the end group substitutions, and the molecular mass for PBzE dendrimers[26].

**C. Dielectric spectroscopy (DS) :** Dielectric spectroscopy gives information about molecular dynamic processes in polymers (a-, h-, g-,and y-relaxation).

## Pharmaceutical Application of Dendrimers:

### 1. Dendrimers in drug delivery:

Dendrimers have been utilized to carry a variety of small pharmaceuticals and biotechnological molecules. Encapsulation of the well-known anticancer drug cisplatin within PAMAM dendrimers gave conjugates that exhibited slower release, higher accumulation in solid tumors, and lower toxicity compared to free cisplatin[27]. Similarly, the encapsulation of silver salts within PAMAM dendrimers produced conjugates exhibiting slow silver release rates and antimicrobial activity against various Gram positive bacteria[28-30]. In another study, PAMAM dendrimers with 4, 8, and 16 terminal ester groups were converted to hydroxy-terminated molecules using TRIS to reduce their potential cytotoxicity. These dendrimers were able to encapsulate small acidic molecules such as benzoic acid and 2,6-dibromo-4-nitrophenol in 1:1 and 2:1 (drug :dendrimer) ratios but did not form a complex with the non-acidic drug tioconazole. Presumably, the guest molecules were retained within the dendritic branching clefts by hydrogen bonding with interior protonated amide groups. Therefore, the inclusion complexes were observed to separate after deprotonation of these amide groups at pHb7[31]. Two polyester-based dendrimers (generation 4 with trisphenolic core) were synthesized, one carrying a hydroxy surface, the other a tri(ethylene glycol) monomethyl ether surface. These dendrimers were compared to a 3-arm poly(ethylene oxide) star polymer, carrying G=2 dendritic polyester units at the surface. The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h). Therefore, the anticancer drug doxorubicin was 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[32].

### 2. Dendrimers In Gene Transfection:

Dendrimers can act as vectors, in gene therapy. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of 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[33]. A transfection reagent called SuperFectTM consisting of activated dendrimers is commercially available. 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 not only be due to their well-defined shape but may also be caused by the low pK of the amines (3.9 and 6.9). The low p*K* permit the dendrimer to buffer the pH change in the endosomal Compartment[34]. 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[33].

### 3. Dendrimers as biomimetic artificial proteins:

Based on their dimensional length scaling, narrow size distribution, and other biomimetic properties, dendrimers are often referred to as artificial proteins[35-39]. Within the PAMAM family, they closely match the sizes and contours of many important proteins and bioassemblies. For example, insulin (3 nm), cytochrome C (4 nm), and hemoglobin (5.5 nm) are approximately the same size and shapeas ammonia-core PAMAM dendrimers generations 3, 4 and 5, respectively. Furthermore, generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of biological cells, while a generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes. These duplexes form stable complexes with histone clusters to condense and store DNAwithin the nucleosome of cells. Undoubtedly, the close match in size and shape between histone clusters and PAMAM dendrimers of generations 7–10 accounts for the extraordinary stability of DNA–PAMAM complexes, as well as the enhanced gene expression observed for these dhistone mimicsT compared with lower generation (G=1–5) PAMAM dendrimers[40-42].

### 4. Dendrimer as Solubility Enhancers:

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers having a hydrophobic core and a hydrophilic surface layer, have been termed unimolecular micelles. Unlike traditional micelles, dendrimers do not have a critical micelle concentration. This characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure at all concentrations of dendrimer. 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[43]. After phospholipid coating of the dendrimer–fatty- acid macromolecule, oral bioavailability in rats of 5-flurouracil was nearly twice the level of free 5-flurouracil . Dendrimer-based carriers could offer the opportunity to enhance the oral bioavailability of

problematic drugs. 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[44].

### 5. Dendrimers as ophthalmic vehicles for ocular delivery:

The use of aqueous PAMAM dendrimers has been shown to be of interest in the ocular route. Indeed, PAMAM dendrimers demonstrated physicochemical characteristics (pH, osmolality, viscosity) which are compatible with ocular dosage form formulations. The results suggest that, in addition to size and molecular weight, charge and molecular geometry of bioadhesive dendrimers also influence ocular residence time. The undoubted advantage of these polymers is the prolongation in corneal residence time which they induce and the increased bioavailability of drugs incorporated in eye drops. The pharmacodynamic observations highlighted greater bioavailability for drugs when DG1.5 and DG4.0(OH) dendrimers with carboxylate and hydroxyl surface groups, respectively, are combined with the eye drops. This kind of systematic approach to characterizing the influence of the physicochemical properties of polymeric macromolecules on residence time, will aid the design of novel polymeric biomaterials with prolonged-release profiles for the ocular route[45].

### 6. Dendrimer in transdermal drug delivry:

Dendrimer designed to be highly water soluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulation and to deliver drug efficiently. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) could be improving the drug permeation through the skin as penetration enhancers[46].

### 7. Dendrimer in Pulmonary drug delivery:

Dendrimer have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40% [47].

### 8. Dendrimers in Targeted drug delivery:

Dendrimers have ideal properties which are useful in targeted drug delivery system. One of the most effective cell specific targeting agents delivered by dendrimers is folic acid and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothicyanate for targeting the tumor cells and imaging respectively[48].

### 9. Dendrimers in Imaging:

Imaging modalities can be used in oncology to diagnose, locate, stage, plan treatment, and potentially find recurrence. Computed tomography (CT) and magnetic resonance imaging (MRI) are two standard methods of imaging associated with cancer diagnoses[49,50]. Gadolinium (Gd) paramagnetic contrast agents for MRI have been complexed with dendrimer molecules over the last two decades for contrast enhancement. Gadolinium contrast agents have been conjugated to PPI and evaluated for use as macromolecular MR contrast agents[51].

## Conclusion:

The high level of control over the dendritic architecture makes dendrimers ideal carriers in drug delivery applications. In most cases, the size of the dendrimer is an important parameter, and the dendrimeric structure often offers dramatic improvements compared to monomeric compounds. . Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs and also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production.

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**Figure No. 1: The Dendritic Structure**

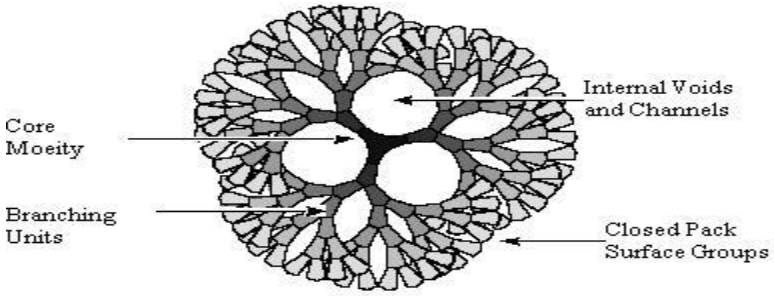


**Figure No. 2: Synthesis of Dendrimers**

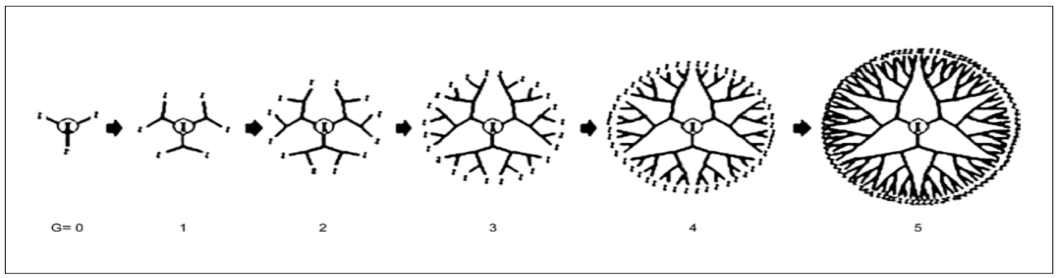


**Figure No. 3: Divergent Synthesis of Dendrimer**

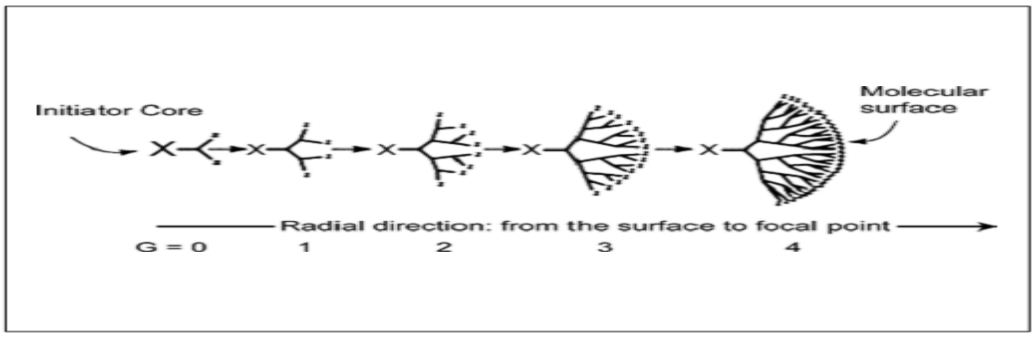


**Figure No. 4: Convergent Synthesis of Dendrimer**