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Dendrimers- A Emerging Tool For Drug Delivery

Shyma M.S*, Sheri P.S
Department Of Pharmaceutics, Mar Dioscorus College of Pharmacy Alathara, Sreekaryam, Thiruvananthapuram, Kerala, India

Abstract

Dendrimers are interesting with in the field of biomedical applications thanks to their unique characteristics. Dentrimers are the hyper branched, well-defined globular structure. It contain multi valency, variable and tunable chemical composition, and high biological compatibility. These are the main characteristic feauters. Specifically, it's important to notice that the tri dimensional architecture of dendrimers allows the incorporation of biologically active agents to create the corresponding conjugates. During this context, this review focuses on outline of dendrimers as drug delivery systems like wise because the benefits ,challenges and there for the application of dendrimers.

Key Words: Dentrimers, Types, Drug Delivery, Application

INTRODUCTION

Dendrimers, also called cascade polymers, they are tri dimensional structures that were first reported in 1978 [1]. These uni molecular micelles were also the idea for polypropylene imine (PPI) dendrimers, constructed in the 1990s. In 1983, Tomalia et al. also reported an awfully interesting form of dendrimer prepared from a combination of amines and amides, which are called poly (amido amines) or PAMAM dendrimers. A dendrimer is composed of three different topological parts that are focal core, building blocks with several interior layers composed of repeating units and multiple peripheral functional groups. The term dendrimer, first proposed in 1985, is derived from the two Greek words 'dendron' (tree branch-like) and 'meros' (part of), and was chosen due to their structural shape.

Due to the poor solubility of the drug with in the body's aqueous environment, the therapeutic effectiveness of some drugs is usually limited by its inability to achieve access to the site of action in an appropriate dose. To overcome this drawback, an excellent number of dendrimer structures are developed and investigated supported inspiration from biological systems for biological and drug-delivery applications during the past twenty years. Furthermore, many reports on analysing the drug holding capacity of dendrimers, whether physically loaded or chemically linked, and their ability to release in a very controlled manner is available. They offer distinct advantages of mono dispersity and multi valency as drug-delivery vehicles, which are dependent upon their size, generation and surface functional groups. Furthermore, their well-defined structure might decrease the uncertainty related to the molecules' shape and size and also increase the accuracy of drug delivery. Consequently, greater possibilities can be explored by using dendrimers as gene-delivery vehicles.

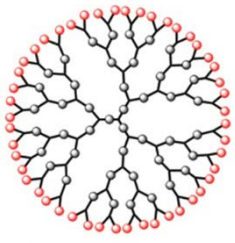


Fig. 1 Basic structure of dendrimer

Dendrimers as nanostructured macromolecules have ideal capabilities in entrapping and/or conjugating the high molecular weight hydrophilic/hydrophobic cargos by host-guest connections as well as covalent bonding, respectively. Besides, dendrimers are recognized for their distinct buildings, flexibility in drug delivery, and high functionality whose possessions resemble with biomolecules. Dendrimers can be used to deliver nucleic acid-based drugs such as siRNA, shRNA and miRNA alongside chemotherapeutic agents into cells with no damaging or deactivating effects on the DNA. For selective targeting of drugs into carcinoma cells, Dendrimers are three‑dimensional, immensely branched structure. It is well‑organized nanoscopic macromolecules (typically 5000‑500,000 g/mol). It possess low polydispersity index and have displayed an essential role in the emerging field of nanomedicine.

ADVANTAGES OF DENDRIMERS

- It improves bioavailability.
- It helps to overcoming of cellular barriers.
- It is cite specific drug delivery.
- It provides controlled drug release.
- It produces better patient compliance.
- It increased solubility, stability, and permeability of medication.
- It reduced macrophage uptake.
- The facile passage across biological barriers by trans cytosis.
- It show improved delivery efficiency.
- The capability to deliver a spread of medication.
- It used as viral diagnosis.
- It has ability to keep up drug levels in a very therapeutically desirable range.
- It increased half-life.
- It increased drug retention and providing extended therapeutic effects.(E.g. ocular drug delivery)
- It helps to reduce side effects by targeted delivery.
- They have low toxicity and low immunogenicity.
- It shows high uniformity and purity.
- It provides rapid cellular entry.

TYPE OF DENDRIMER

PAMAM (Poly Amido Amine) Dendrimer

- It synthesized through the divergent procedure.
- Ammonia or ethylene diamines are used as initiator core of the dentrimer.
- Condensation of DNA followed by transfection attributable to possess positive surface.

PPI (Poly Propylene Imine) Dendrimer

- These are Amine terminated hyper-branched macromolecules.
- It synthesized by divergent approach.
- 1, 4-diaminobutane is employed as the dendrimer core.
- Some other molecules with primary or secondary amine groups may be utilized as core in theirsynthesis.

Liquid crystalline (LC) dendrimers

- It Consist of mesogenic LC monomers.
- This usually designed by rod-like (calamitic) or disk-like (discotic) molecules.

Core Shell (tecto) dendrimers

- It Possess a well-ordered structure because of controlled covalent bond of building blocks.
- It composed of a core dendrimer that will or might not contain a cargo.
- These have simple synthesis procedure.

Chiral Dendrimer

- These Have different construction of constitutionally but are chemically similar with a chiral core.
- Chiral, non-racemic dendrimer are proper for applications in asymmetric catalysis and chiral molecular recognition [2].

Hybrid dendrimers

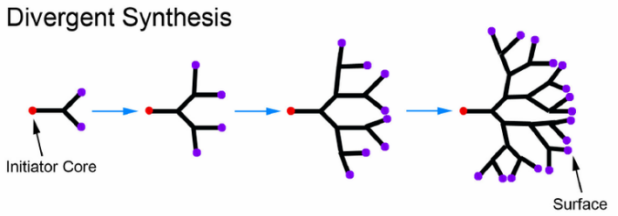
- The Combination of dendritic and linear polymers in hybrid blocks or graft copolymer systems.
- They are applied as surface active agents, compatibilizers or adhesives, or hybrid dendritic linear polymers as a result of the little dendrimer segment coupled to multiple reactive chain ends provides a chance to use them [3].
- It Can produced from various polymers with dendrimers generated the compact, rigid, uniformly shaped globular dendritic hybrids.

SYNTHESIS OF DENDRIMERS

Mainly three approaches are used for synthesis of dentrimers.

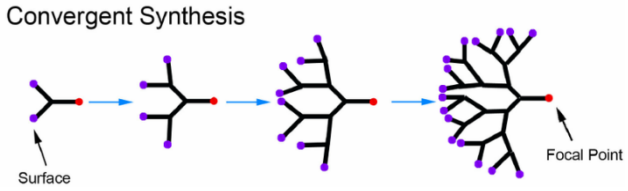
1. Divergent approach

The divergent approach arose in the early 1980s [4]. The fundamental operations carries with it coupling step and activation step. Coupling step introduces a replacement 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. In the dentrimers structure exponentially increase the number of surface functionalities because of the continuously increases the number of generations of dentrimers. That is a scientist , assuming that, the construction of ideal dendrimers not affected the steric hindrance , active site accessibility and the monomer's functional group(s), this process permits the exponential growth of free active sites per generation . The excess monomer loading and lengthy chromatographic separations are required for create high generation dentrimer but it can be quite difficult to achieve, even with highly efficient reactions. This approach is currently the preferred commercial route used by producers worldwide. The synthesis of PAMAM could be a typical example. PAMAM dendrimers have several amine, carboxylic and hydroxyl surface groups , they are liquid or semi-solid polymers .They were synthesized on the idea of two consecutive chains forming reactions, the exhaustive Michael addition reaction and also the exhaustive amidation reaction, repeating alternatively.



2. Convergent Approach

The convergent approach is another method for producing precisely controlled dendritic architectures [4]. Within the convergent approach, the branching architecture originates from what is going to become the dendron molecular surface and precedes to wards a reactive focal point, resulting in the formation of a one reactive dendron [5]. Like to the divergent approach, its basic operations also consist of coupling step and activation step. It provides greater structural control than the previous approach. At each growth step it has relatively small number of simultaneous reactions, it produce unmatched purity and functional versatility product. In fact, the convergent approach is generally limited to the development of only lower generation dendrimers due to the nano scale steric issues that are encountered when attaching the dendrons to the molecular level core. For instance, the synthesis of poly (aryl ether) dendrimers as developed by Hawker and Fréchet .



3. Other Approaches

This approach reduced the number of synthetic and liquid chromatographic steps required in the synthesis and purification of the final dendrimers. The acetonide, hydroxy, acetate, n-octanoate, n-palmitoate and benzoate end-functionalized dendrimers showed large differences in thermal and solution behavior counting on the character of their end-groups. The acetate-terminated dentrimer glass transition temperature is $-4^{\circ}C$ and for the hydroxyl-functionalized dendrimer transition temperature is $+57^{\circ}C$. Terminated with long alkyl chains dentrimer were highly

soluble in hexane and dichloromethane and poorly soluble in water and methanol, whereas the hydroxy-terminated dendrimer showed the opposite solution behaviour. All surface-modified dendrimers were amorphous in keeping with differential scanning calorimetry (DSC), apart from the n-palmitoate-terminated dendrimer, that showed a distinct melting transition at+28◦C in its DSC trace thanks to the crystallization of the long alkyl chains[6] .

DRUG DELIVERY SYSTEMS SUPPORTED DENDRIMERS

An extremely branched building is often used as an appropriate targeted drug delivery carrier through attaching different ligands. Outstanding possessions of dendrimers are to blame for their great advantages comparing to other delivery systems. The three-dimensional construction alongside with multifunctional terminal groups yet as numerous internal cavities let dendrimers to move different cargoes. These cargoes can capture within the scaffold or attached to the surface of dendrimers. These structures are known by high loading efficiency yet as stability in path of intracellular transportation. In keeping with literature, dendrimers can progress drug's solubility, spread the cargo's blood circulation time through decreasing their removal, preserve drug concentrations on top of the minimal therapeutic dose with in the plasma, and protect them from probable environmental damages. Dendrimers as systems proper for drug delivery can apply to avoid the resistance mechanisms and simplify the carriage of the drug on to target cells without involving normal cells [7]. From some point of views, dendrimers are different compared to standared polymers; they 're in nano-meteric size and spherical shape that own a high grade in uniformity of molecular structure, and tolerate of high surface modifications . An oversized drug capturing may also confer by the unique structural configuration of dendrimers . Such a cargo loading may perform through numerous methods like the surface adsorption (that enjoy ionic interactions), entrapment within micro cavities, or direct covalent bonding to the surface functional groups. These outstanding possessions convert dendrimers to an ideal system for simultaneous delivery of both hydrophobic and hydrophilic medicament. The potential applications of dendrimers in medicine have made considerable attention during in this regards. As an example, there are numerous alterations of dendrimers's exterior groups which enable to realize antibody or peptide conjugates with, or to make dendritic boxes that capture guest molecules. Poly (amidoamine), or PAMAM, is possibly the foremost famous dendrimer.

CHALLENGES OF USING DENDRIMERS IN DRUG DELIVERY

Some properties of surface groups like charge affect the cytotoxic action of dendrimers. Irrespective of surface composition and molecular structure, cationic dendrimers are more cytotoxic and hemolytic than anionic and neutral dendrimers, because of their non-specific affinity to cell membranes with negative charge. Their toxic effect is generation-dependent and increases with the number of surface groups [7] while neutral and negatively charged dendrimers do not show cytotoxic effect in vitro. To enable diagnostic and therapeutic uses, it is required to decrease the toxicity of positively charged dendrimers. To the present end, some chemical alterations of terminal groups are presented which improve the targeting potential, meaningfully extend blood half-life, improve bio-distribution and biocompatibility pattern of dendrimers.

PROPERTIES OF DENDRIMERS

Dendrimers are one amongst the simplest recognized NPs thanks to unique properties like symmetrical structure, spherical shape, monodispersed, and branched structure. There are three main parts with in the structure of a dendrimer; a central core, branches, and functional end groups on the surface. All three parts has reported to indicate critical functions, affecting the dimensions, shape also because the other features of the dendrimers. The generation of a dendrimers denotes to the amount of repeated branching cycles that are formed throughout its preparation. For example, if the branching is completed onto the core molecule 3 times, the prepared dendrimer may be a third-generation kind (G3) [8]. Figure 1 shows a G4 dendrimers structure with differing types of targeting ligands in several sections of dendrimer.

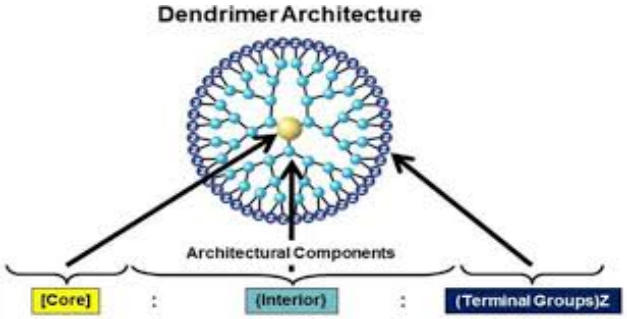
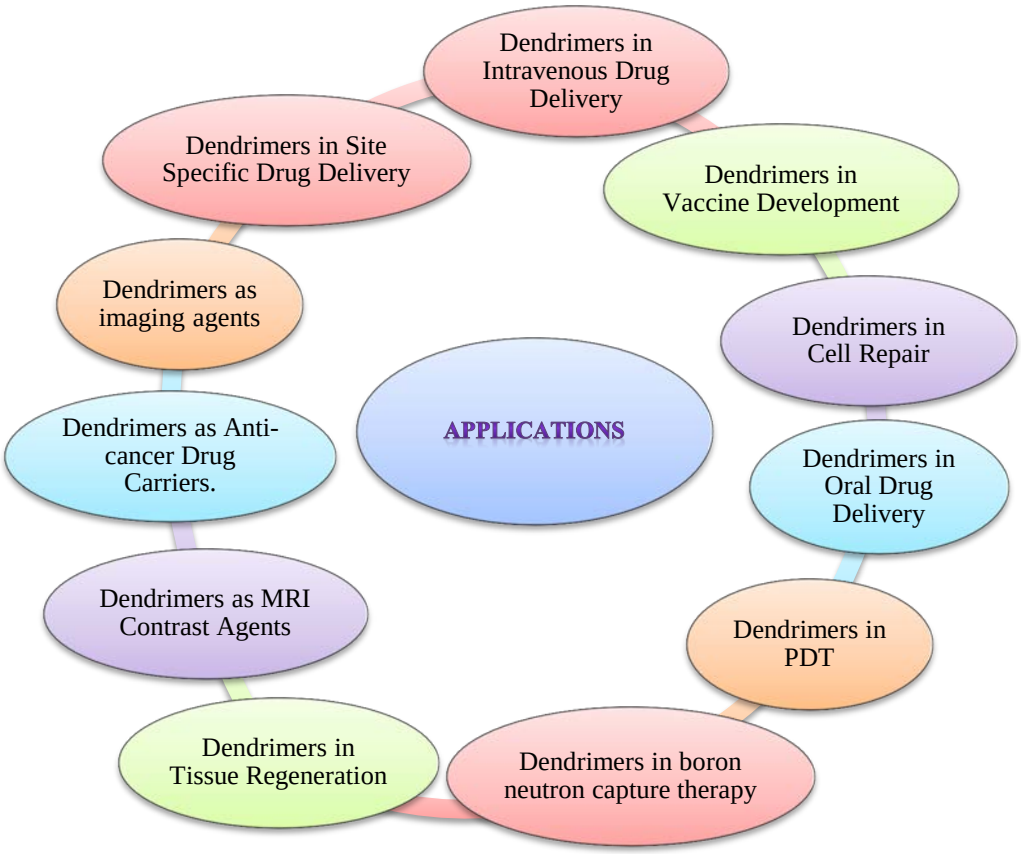


Figure2. Architecture of a dendrimer.

Comparing to other polymeric architectural systems dentrimers show many advantages. The characteristics of branched macromolecules in dendrimers are completely different from current linear polymeric materials. The dendrimers preparation methods are ready to generate homogeneous structures with uniform molecular mass. Due to the spherical form also as interior cavities, dendrimers are called "host-guest" molecules, that they will display great encapsulation capabilities with the flexibility to deliver several compounds in their interior. These structures are composed of 2 or more molecules that are kept together in inimitable structural connections. The forces aside from full covalent bonds are involved among them. Chemical and biological possessions of the dendrimers rely upon surface terminal groups. The high number of surface functional groups has reported to be chargeable for high solubility similarly as permeability of dendrimers. Sometimes, the terminal groups are extremely reactive and so might have to further alterations. Post-modification of the surface of the macromolecule is performed either to vary the physicochemical possessions or to form a particular activity like catalytic or therapeutic.



APPLICATIONS

- **Dendrimers in boron neutron capture therapy**
  Boron therapy is anxious with the treatment of cancers that's supported Boron capture reaction [9].The applicability of PAMAM dendrimers in investigating intratumoral delivery of agents for neutron capture therapy is remarkable in bioscience.
- **Dendrimers in PDT**
  PDT refers to treatment of tumor cells by photosensitizers that on irradiation of sun shine of appropriate wavelength pass their excess energy to nearby molecular oxygen to make reactive oxygen species like singlet oxygen and free radicals which are toxic to cells and tissues. Dendrimers are used as promising carriers for improved delivery of 5-aminolevulinic acid (a natural precursor of photosensitizer protoporphyrin 1X) that increases the build-up of porphyrin in cells, which further ends up in toxicity. Recently, polymeric micelles encapsulating dendrimer phthalocyanine are developed as a photosensitizer formulation for enhanced photodynamic effect [10].
- **Dendrimers as imaging agents**
  Visualizing both tumor vasculature and lymphatic involvement using Gadolinium (III) (Gd) the paramagnetic contrast agent. Biodegradable tumor targeting contrast agent has been developed from Gd chelates and PEG conjugated polyester dendrimer. This dendrimer conjugate contrasting agent has shown to supply enhanced contrast than commercially available product Magnevist®. Furthermore, its retention altogether the organs was low leading to reduction of Gd induced toxicity [11].
- **Dendrimers as Anti-cancer Drug Carriers.**
  The most promising uses of dendrimers areas drug carriers due to their globular shape and their combined hydrophobic and hydrophilic character. In this way, properly positioned functional groups in the internal or peripherical zone can retain organic and inorganic compounds by means of dynamic supra molecular interactions [12], those found in DNA .
- **Dendrimers as MRI Contrast Agents**
  Magnetic resonance imaging (MRI) is widely accustomed obtain tri dimensional images in vivo without radiation. Employing a gadolinium chelate contrast agent, super paramagnetic iron oxide particles and hepato biliary contrast agents are administered before the scan. Among the most properties that are required for contrast agents, the necessity to diffuse rapidly from blood vessels into the interstitial space and to be efficiently excreted from the body without accumulation are two of the foremost important [13].
- **Dendrimers in Tissue Regeneration**
  Tissue regeneration technology consists of promoting the healing or construction of living tissue for organs, which may successively be utilized in transplant procedures [14]. To do so, biocompatible matrices are

necessary to support or encapsulate cellular material in order that the living cells can have access to nutrients and eliminate metabolic waste. Among the natural polymers that are explored for tissue regeneration, collagen , fibrin , hyaluronic acid , chondroitin sulfate , alginate , dextran , and chitosan stand out because the most popular materials due to their biocompatible nature and their availability. in the case of synthetic polymers, both linear and three-dimensional polymers are studied. To this end, linear polymeric chains such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (capro lactone)(PCL), and poly(ethylene glycol) (PEG) have been explored **.**

- **Dendrimers in Oral Drug Delivery**
  The oral route of drug delivery normally is taken into account the favourite means of drug administration the oral route remains the well liked route for administration of therapeutic agents due to accurate dosage, low cost therapy, self-medication, useful for children and geriatric patients, non-invasive method and simple administration resulting in high level of patient compliance. It is suitable candidate in oral drug delivery because it loosened the tight junctions of epithelial layer and thus an improvement within the absorption of small relative molecular mass drugs was achieved [15].
- **Dendrimers in Intravenous Drug Delivery**
  The intravenous route is the simplest method for delivering a drug into the circulation. However, poor water solubility of the many drugs, especially anti-cancer drugs, limits the applying of intravenous administration route in clinical trials. Intravenous administration of those drugs leads to several side effects, like hemolysis and phlebitis. Much effort has been made to develop new formulations that are suitable for the intravenous route, among which dendrimer-drug formulation is attracting increasing interests mutually of the emerging delivery systems. Their bio distribution in the body and toxicity or immunogenicity must be considered before the proposed application of dendrimers in the intravenous route. Meanwhile, *in vivo* bio distribution of dendrimers after intravenous administration has also been intensively studied. Kukowska-Latallo *et al.* [16] investigated the bio distribution of tritium labelled G5 PAMAM dendrimers after intravenous administration and located these materials were cleared rapidly from the blood via the kidney during the primary day post injection.
- **Dendrimers in Site Specific Drug Delivery**
  In the targeted drug delivery concentrate the drug within the tissues of interest and reducing the relative concentration of the medicament within the non-targeted (remaining) tissues. And the drug is localised on the targeted site. Hence, surrounding tissues are't laid low with the drug. The targeted delivery of chemotherapeutics is important to scale back the side effects significantly related to conventional therapy, where healthy tissues like liver, spleen, kidneys and bone marrow can accumulate the toxic levels of drug. The location specific delivery of the drug might be achieved by surface modification of dendrimers employing various targeting moieties like folic acid (FA), peptides, monoclonal antibodies and sugar groups [17].
- **Dendrimers in Vaccine Development**
  Vaccination undoubtedly has been one amongst the foremost important and successful strategies implemented worldwide for the control different types of infectious diseases. With In the field of vaccine design, dendrimers may be used as model molecules to host immune +-stimulators and/or antigens [18].
- **Dendrimers in Cell Repair**
  For porous polymeric extracellular matrices (ECMs) [19] which will accommodate and provide a correct environment to repair tissues, dendrimers are utilized in *in vivo* studies. The regeneration of porcine tissue Poly amido amine dendrimer generation 1.0 is used. Another application of dendrimers during this field corresponds to *in vitro* bone tissue reconstruction.

CONCLUSION

Outstanding properties of dendrimers like their size, shape, branching ability, and their surface modifiability convert these compounds to an ideal vehicle in different medical fields such as drug/gene delivery. The unique properties of dendrimers provide diversity of applications.

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