

DENDRIMERS IN NOVEL DRUG DELIVERY SYSTEM: AN UPDATED REVIEW

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Abstract

Nanoscale molecules known as dendrimers possess clearly defined, uniform, and monodisperse structures. They're composed of a symmetrical core with an outside and interior shell. Due to their multiple beneficial features, dendrimers are an excellent choice in the medical field; this page compiles all of their different uses. Many different kinds of poly (propylene imine) and poly (amidoamine) dendrimers integrated with imatinib, sunitinib, cisplatin, melphalan, doxorubicin, paclitaxel, and methotrexate have shown advantages over the drug molecule alone. Dendrimers have undergone extensive research for their potential as anti-cancer agents. The mainstay of the inflammatory medicine was dendrimer complexes of indomethacin, piroxicam, ketoprofen, ibuprofen, and diflunisal. Given the circumstances, the growth of bacterial strains resilient to antibiotics, fluoroquinolone, macrolide, beta-lactamine, and aminoglycoside dendrimer complexes have shown positive outcomes. In relation to treatment with antiviral drugs, There has been a study to create dendrimers being conjugated with tenofovir, maraviroc, zidovudine, oseltamivir, and other antivirals. Additionally, dendrimers have successfully allured much interest in cardiovascular medicine. Large, multi-component macromolecules constitute dendrimers. The present review enlists all kinds of related scientific and valuable aspects of dendrimers to help the researcher working with dendrimers.

Keywords: Dendrimer; Drug Therapy; Nanoscale; PAMAM; Pseudo Rotaxane; Targeted Release

Introduction

Dendrimers have a spherical shape and a three-dimensional architecture that resembles a little tree. The word "Dendrimers" pertains from the Greek word "Dendron" (Steinman, 2007), which is often used to refer to a tree because of its branching structure. The first Dendrimers were developed in 1978 by Buhleier *et al.*, who were successful in constructing a repetitive arrangement which was cascade-like of mono and also diamine around the

outside of their central core (Nathan *et al.*, 2012). The second class of synthesized macromolecules, dubbed "arborols," is referred to by the Latin term "trees." It is also possible to refer to dendrimers as "cascade molecules," albeit the word "dendrimers" is more popular. (Klajnert *et al.*, 2001). Dendrimers can be said to be almost monodisperse like macromolecules, having branching units that are symmetrical and are built around a molecule that is

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tiny in structure or a polymer having a linear core (Newkome *et al.*, 1985; Tomalia *et al.*, 1985; Tomalia *et al.*, 2002). Dendrimers can be said to be à nonchemical molecules but rather an architectural theme. As the number of generations has increased, polyionic dendrimers can be altered in their sizes, shapes, and flexibility because they do lack a permanent form (De Gennes *et al.*, 1983; Hawker *et al.*, 1990). A large number of functional groups combined with a molecular structure that is compact defines dendrimers, which bear artificial macromolecules with a precise molecular structure. In this review, collective information has been portrayed on dendrimers as a novel drug delivery system for better bioavailability and efficacy of pharmaceutical entities.

Structure and Chemistry

Dendrons, the arms that emerge from the central core of a dendrimer, make up the structure. Dendrimers typically include three crucial components: (1) Central core, Mostly, these units are simplified as radially homocentric layers being known as the term generations, (2) Units that were repeated and subsequently connected to the core in the center (3) a functional group being present at the perimeter of the dendrimer utilized to controls its biocompatibility and pharmacokinetic characteristics (Frechet *et al.*, 2001).

Dendrimers can be classified as a brand-new family of the polymeric molecules and being a type of most fascinating and rapidly developing field of innovative chemistry. The chemistry of dendrimer has its own terminology and abbreviations, much as other specialized research areas. In addition, à succinct structural nomenclature is employed to explain the many subsequent chemical reactions being conducted at the surface of the signified dendrimer. Dendrigrfts, a kind of dendritic polymers, will be produced with either a highly defined or monodisperse molecular structure. One among the first suggested dendrimers application was being implied to be used as container compounds, where the small substrates were bound inside the interior gaps of the dendrimer (Tomalia, 2007). Experiments have employed dendrimers, and also hyperbranched polymers to show the properties of monomolecular micelles.

Synthesis

Dendrimers straddle the line between the chemistry of molecules and polymer chemistry. Due to controlled, sequential synthesis and their repeating, monomer-based structure, they have a relationship to the field of polymers as well as the field of molecular chemistry (Bosman *et al.*, 1999; Majora *et al.*, 1999). Linear, cross-linked, and

branching macromolecular architectural classes are known to create reasonably being products that were polydispersed with a range of molecular weights. However, the production of monodisperse and controlled structured macro molecular designs that were similar to the ones being discovered in the biological systems is possible through the synthesis of dendrimers. (Tomalia, 1995). Typically, a convergent or divergent approach is used to create dendrimers (Maciejewski *et al.*, 1982).

The core of the synthesis of dendrimers is a series of cascade events.

Chemists were familiar with the fundamental cascade or iterative procedures far earlier than they are presently. For example, techniques that were similarly provided the baseline of the peptide being solid-phase synthesizing methodology. The creation of fatty acids is one example of how life has long employed similar recurring mechanisms in biochemical synthetic pathways (Grayson *et al.*, 2001).

Either a divergent or a convergent technique is employed in dendrimer synthesis.

Dendrimer synthesis may be accomplished utilizing two main techniques/methods.

The technique called divergent, which was well known in the past, started with the synthesis at the core of the dendrimer, to which the attachment of the arms took place, and also continued by continuously and methodically adding building components. Starting with the chemical structure that can subsequently form the most outer arm of the finished dendrimer and also the synthetic process can be employed to take a convergent approach. Given that the last and final generation number is subsequently being determined in advance, this approach demands the branches being subsequently synthesized of many necessitate sizes and diameters beforehand every subsequent generation.

Dendrimers in Drug Therapy

Dendrimers in the Treatment of Inflammation

A technical method called nanotechnology has a wide variety of possible uses and will have a big influence on how medicine is practiced. Thus, among the most significant the uses of nanotechnology are in the realm of medicine, or “nanomedicine,” which comprises highly specialized medications for use in clinical settings (Leuner *et al.*, 2002; Lipinski, 2002; Kesharwani *et al.*, 2014). In several studies, dendrimers that were solubilized in water moiety, including the dendrimer called PAMAM or the dendrimer called PPI dendrimers, have been used to improve the

solubility of this family of medicines. (Choudhary *et al.*, 2011; Ullah *et al.*, 2011). Utilizing encapsulation technology, it is feasible to solubilize hydrophobic NSAID molecules while also increasing the bioavailability of NSAIDs since these dendrimers include amino-terminal groups (Ihre *et al.*, 2002). The NSAID molecules that were active in nature and also the dendrimer are the main sites of interaction among the amino groups present among the dendrimer and the carboxyl groups being present in the NSAID (Beezer *et al.*, 2003; Kim *et al.*, 2018; Durocher *et al.*, 2016). The utilization of this NSAID is limited because of its negative impact on the digestive system, causing ulcers, bleeding, and unwanted perforation (Kurtoglu *et al.*, 2005; Bonelli *et al.*, 2011). It derivates with an acidic group at the end of its structure, which improves its effectiveness but also has negative side effects, chiefly ulcers in the digestive tract. (kolhe *et al.*, 2006; Avtiet *et al.*, 2016). When ibuprofen is in the ionized form, PAMAM dendrimers boost the medication's solubility more than sodium dodecyl sulphate micelles do. They do this by adhering to the surface through electrostatic interactions and encasing the medication in the interior cavities through hydrophobic contacts. (Garavito *et al.*, 2002).

By adding a propylene oxide residue (PPO) to the PAMAM dendrimer's core structure, The solubility power of the medications increased along with the dendrimers development due to the bigger nucleus of dendrimer and internal structure, which correlates also to a stronger interaction with the pharmaceuticals in the dendrimers of the PP-PAMAM than the simpler dendrimers of the PAMAM (Ohshima *et al.*, 2014) (Figure 1) Additionally examined was the utilization of dendrimers of PAMAM coupled with NSAIDs for transdermal delivery. Since the solubility was enhanced, transdermal penetration increased. Numerous NSAID compounds, including indomethacin, piroxicam, ketoprofen, and diflunisal, have been examined using this method, with results demonstrating an improvement in the medications' bioavailability (Kesharwani *et al.*, 2014; Weledji *et al.*, 2017).

(NSAIDs can interact with dendrimers composed of (a) PAMAM and (b) PPOPAMAM. Adapted from (Ohshima *et al.*, 2014), which was printed in the 2013 issue of the International Journal of Pharmaceutical Sciences)

Dendrimers in Antibacterial Therapy

Chemotherapeutic chemicals are used in antimicrobial therapy. These medications function against germs in a number of ways; inhibiting the production of amino acids, proteins, or other

products of metabolism or impairing the integrity of membranes are just a few examples. (Tsafnat *et al.*, 2011). They can be beneficial in the management of infections of the bacteria with certain limitations like the fact that the subsequent antimicrobial activity spectrum could be limited, and it also has concerns about the drug's safeness and tolerability (Tsafnat *et al.*, 2011), and incorrect dosing can result in undesirable side effects, allergic reactions, or the subsequent toxicity (Spellberg *et al.*, 2013), inadequate medicinal distributional property and administration, as well as bacterial resistance to antibiotics (Walsh *et al.*, 2013; Karthikeyan *et al.*, 2019).

To increase treatment efficacy and prevent adverse effects, antibiotics can be encased in dendrimeric structures. The main goals of designing dendrimers as systems of delivery were to manage the size of particles, characteristics of surface, functionality, length/density of the branch, and release of the medicament in view to create the desired impact on the selected site of action (Chenget *et al.*, 2007; Authimoolamet *et al.*, 2016; García-Gallego *et al.*, 2017). The dendrimers of PAMAM and PPI are the dendritic polymers that are most often employed in therapeutic applications (McNerny *et al.*, 2010). Dendrimers' multifunctional groups allow them to be conjugated with antibiotics, increasing the action of both substances. PAMAM-NH₂ dendrimers are dendrimer conjugates that are typically from generations two or three. The increasing toxicity of higher-generation Carbosilane dendrimers (G4-G6) further limits their utilization as conjugates with antibiotics. (Lopez *et al.*, 2009). Table 1 provides other illustrations of dendrimers coupled with antibiotics (Lewis *et al.*, 2012).

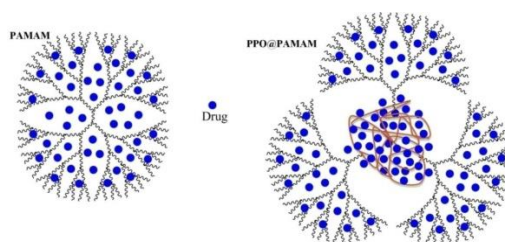


Figure 1. Shows the interaction of NSAIDs with PAMAM and PPOPAMAM dendrimer

Dendrimers in Antiviral Therapy

Numerous substances, including bacteria, viruses, fungus, and other parasites, can have an impact on

human health. Of them, viruses may exploit the enzymatic systems of live cells to proliferate inside living cells (Wróblewska *et al.*, 2015). Dendrimeric conjugates containing active components for antiviral therapy have been the subject of many studies, and they offer a variety of advantages, including improved subsequent specificity and effective subsequent bioavailability, a much longer and effective half-life, and decreased drug toxicological effect (Vacas-Córdoba *et al.*, 2018). Over the past ten years, nanotechnology has been an important methodology for enhancing the properties of antiretroviral medicaments in treatment against the HIV virus (Rasines *et al.*, 2012) using effective dendrimeric nanoparticles with sizes ranging from 1-40 nanometers (Relaño-Rodríguez *et al.*, 2019) and also the different subsequent generations that compiled of G1-S4, G2-S16, and G3-S16. These improved and effective compounds can be recognized with their peripheral groups that were sulfonate as follows: While G1-S4 PCDs have four important and effective peripheral sulfonate groups, G2-S16 and G3-S16 PCDs each have sixteen groups (Arnáiz *et al.*, 2014).

Active ingredient Tenofovir (TFV) and the active ingredient maraviroc (MRV) were tested and assessed in relation to their dendrimer conjugates. The findings conferred that these conjugates can be more effective, allowing for lower doses to have the same therapeutic benefits. This has the potential to minimize toxicological effects and the development of resistance to the drug, confining the viral mutations. The proof of synergism as well as an increase in antiviral potency at the same time. The dendrimers of the very first (G1) and subsequent second (G2) generations (G1-S16, G1-NS16, G2-S16, G2-STE16, and G2-S24P) were evaluated alone and in combination (Sepúlveda-Crespo *et al.*, 2015).

Cardiovascular Therapy with Dendrimers

Due to medicines' poor bioavailability in cardiovascular diseases, conjugates of the subsequent dendrimer have been researched.

Nifedipine has poor water solubility throughout a pH range of about 4 to 13, which limits the bioavailability in the human body. Nifedipine became more soluble in water at a pH of 7 when PAMAM dendrimers containing amine or ester surface functional groups, ranging from G0 to G3, were used. The effectiveness of the ester surface functional groups was higher than that of the amine ones. Therefore, PAMAM dendrimers might operate as nifedipine solubilize to enhance its therapeutic benefits (Singh *et al.*, 2017). Ramipril and hydrochlorothiazide together have been successfully used to treat hypertension. The two-

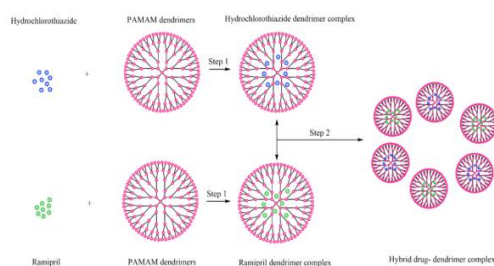


Figure 2. Two-step procedure for getting a hybrid drug-dendrimer complex

step combination of these two medicines was carried out using PAMAM dendrimers. A hybrid drug-dendrimer complex was made by individually encasing both medications in the first stage and combining them into a single formulation in the second phase. (Singh *et al.*, 2016)(Figure 2)

The novel hybrid dendrimer of the Ramipril-hydrochlorothiazide complex formulation could be implied to increase therapeutic utilization by increasing the loading of the drug and enhancing the solubility of the given drug, dissolvability, and stability (Ertürk *et al.*, 2017). Candesartan cilexetil's poor solubility and bioavailability made it a good candidate for dendrimer entrapment investigations. By boosting the production and concentration of the PAMAM dendrimer utilized, the drug's solubility may be improved. The solubility of the compound was greater for dendrimers with carboxyl or tris(hydroxymethyl)aminomethane (TRIS) groups than for those with surface groups of the amine, suggesting that the surface functional groups were involved in this (Kulhari *et al.*, 2017).

Simvastatin solubility and dissolution were shown to be increased in *in vitro* investigations using PAMAM dendrimers. This was reliant on the pH of the solution, the dendrimer concentration, and the functional groups that were accessible to it. Simvastatin-dendrimer complexes can also offer the medication's regulated release. Dendrimers of the PEGylated PAMAM-G4 showed improved solubility capacity, subsequent dissolution capacity, effective stability, and also biocompatibility in contrast to non-PEGylated dendrimers. They also showed a delayed release of simvastatin (Ferlay *et al.*, 2019).

(Adapted from (Ertürk *et al.*, 2017), which was released by the European Journal of Pharmaceutical Sciences in 2017.

Dendrimers in Cancer Treatment

Cancer, which can be defined as the uncontrolled growth of cells brought on by a range of modifications brought on by physical, chemical,

biological, or genetic causes, is responsible for a sizable portion of morbidity and death. An imbalance between cell proliferation and death leads to the development of cancer into cells that invade distant sites. Despite continued scientific efforts over the past many years to find the subsequent effective treatment, cancer confers to become one of the leading death reasons. (He *et al.*, 2013). Traditional antineoplastic therapy has several serious side effects. Radiation that is often administered might cause secondary gene modifications that could lead to problems and subsequent future malignancies. Chemotherapy, subsequent immunotherapy, and also effective gene therapy frequently have significant no specificity, which lowers the drug's absorption at the cancer site (Zitvoget *et al.*, 2013; Castro *et al.*, 2018). When a medication molecule is transported to cancer tissue across several biological compartments by dendrimers, the pharmacodynamic activity at the target location is maximized. This benefit of dendrimers makes it a crucial tactic in the treatment of cancer (Medina *et al.*, 2009). Drugs being released from the complex of the subsequent dendrimer are controlled and reviewed by a variety of processes, including degradable spacers at certain locations and quantitative terminal group variation (Noriega-Luna *et al.*, 2014; Srinivasan *et al.*, 2015). Numerous investigations have shown the existence of intramolecular connections between dendrimers and compounds often used in antineoplastic therapy, including paclitaxel (PTX), camptothecin (CPT), methotrexate (MTX), 5-fluorouracil (5-FU), and doxorubicin free base (DOX). These compounds have a low hydro solubility and a high non-specific toxicity, which are their two main downsides. Consequently, using dendrimers is a potential tactic. (Jhong *et al.*, 2016; Choudhary *et al.*, 2017).

PAMAM, or poly (amidoamine) dendrimers

Several drugs used to treat neoplastic diseases have frequently been conjugated with poly (amidoamine) dendrimers:

The fourth (G4) generation of PAMAM dendrimers has been connected to the anticancer drug doxorubicin (DOX), which is used to treat lung and brain cancers. The subsequent conjugation was carried out via the dendrimer surface acyl hydrazone bonds under subsequent guidance of pH-controlled DOX-PEG-PAMAM dendrimer, which improved therapeutic effectiveness and action specificity in lung cancer (Kale *et al.*, 2007; Dichwalker *et al.*, 2017). To demonstrate the existence of gastrointestinal tumors, PTX was linked with a PAMAM-G4-DHA dendrimer grafted with an omega-3 fatty acid. A boost in pharmacological activity in the upper gastrointestinal neoplasm has

been demonstrated when comparing this type of conjugation to the cytotoxic molecule alone (Yao *et al.*, 2018). The cytotoxic effect of a biotinylated PAMAM dendrimer-PTX combination against ovarian cancer was evaluated on OVCAR-3 and HEK293T cells. The PAMAM NH₂ dendrimer-PTX complex is biotinylated, which enhances the pharmacokinetics by enhancing not only absorption by the cell but also being effectively released up to the duration of 72 hours with less toxicity of the cell. This was demonstrated to be true when the effectiveness of the combination was contrasted to that of the medication alone during experimental testing (Choi *et al.*, 2004; Bazak *et al.*, 2015).

In order to boost tumor targeting and minimize systemic harm, the surface PAMAM dendrimers of the medication docetaxel (DTX) have been changed (Kulhari *et al.*, 2016). The boost in efficacy can be seen by the example of DTX, which is used to treat breast cancer. By encapsulating the molecules that are active in nature of trastuzumab-modified DTX (TZ) on the dendrimer surface of the PAMAM G4 of the medicine and using linker to be PEG, this medication was rendered more potent. This conjugation optimizes the DTX-TZ dendrimer complexes' specificity on HER-2 positive cells when compared to the DTX dendrimer (Chung *et al.*, 2016).

Cisplatin (CIS), a chemotherapy medication employed to treat cancers of the breast and ovary, was effectively and subsequently conjugated with the Herceptin active molecule and diglycolamic acid (DGA) to form a dendrimeric complex of the Herceptin-DGA-G4-CIS type (Markowicz *et al.*, 2012). Studies conducted in vitro using Herceptin-DGA-G4-CIS in HER-2 human ovarian cancer cell lines have demonstrated that these complexes have outstanding features, decreasing the half-maximal concentration of inhibition and enhancing neoplastic cell death when compared to the dendrimeric conjugate DGA-G4-CIS and the CIS molecule alone (Karthikeyan *et al.*, 2015; Hou *et al.*, 2016; Abedi-Gaballu *et al.*, 2018). The findings showed that the interaction between the two molecules in this conjugate provides a higher level of action specificity than the two molecules working independently (Esfand *et al.*, 2001; Kannan *et al.*, 2014). In general, the existence of the effective primary amine terminal groups and the subsequent tertiary propylene amines inside the PPI structure characterizes poly (propylene imine) dendrimers. These dendrimers mainly function through improving the conjugated drug's solubility through electrostatic interactions (Kannan *et al.*, 2014). The main advantages of these dendrimers are their high functionality, variety in drug delivery, and straightforwardness of surface modification, all of

which permit the formation of high-generation dendrimers (Tack *et al.*, 2014).

Poly-L-lysine dendrimers (PLL)

One of the first polymers that is subsequently cationic to be employed in complexes and to release DNA was poly-L-lysine (PLL) dendrimers (Al-Jamal *et al.*, 2013). However, PLLs are rarely used for conjugation with different active drug molecules due to their high cellular toxicity and low efficacy (primarily the lack of endosomal escape). In order to boost the DOX molecule, which subsequently has active penetration into multicellular spheroidal prostate cancer cells, DOX, a PLL G6 cationic dendrimer compound, was developed (Bugno *et al.*, 2014). This improved the drug's deadly effect and delayed the proliferation of neoplastic cells (Servin *et al.*, 2018). Cu (II) complexed dendrimer demonstrated selectivity by having an inhibitory concentration (IC₅₀) that was several times higher than uncomplexed dendrimer (on a number of non-cancerous cell lines) and known to inhibit-proliferative activity of a minimum of 80% on KB and HL60 line cells at 1 M (Brahmi *et al.*, 2013; Vanerio *et al.*, 2019).

Cons of Dendrimers as a Novel drug delivery system.

Dendrimers sometimes cause cytotoxicity, and numerous studies have been conducted to investigate dendrimer cytotoxicity in various mammalian cell lines. These attempts, albeit not definitive, have suggested that the level of dendrimer cytotoxicity may be affected by dendrimer chemical makeup and surface functioning, production, concentration, exposure period, cell-medium composition (e.g., serum concentration and type), and cell type under study. Nonetheless, the mechanisms of dendrimer cytotoxicity are poorly known. In general, amino-terminated dendrimers have higher cytotoxicity (as measured by cell viability) than PEGylated dendrimers and species with OH (including TRIS), pyrrolidone, and anionic (e.g., carboxyl) functionality of the same generation and concentration (Stasko *et al.*, 2007).

A research using a range of melamine-based dendrimers with amino, guanidine, carboxyl, sulfonate, phosphonate, or PEGylated functionalities demonstrated the significant cytotoxicity impact of cationic dendrimers (Chen *et al.*, 2004). There have been several publications on dendrimer hemolytic activity, with hemolysis increasing in a dendrimer generation- and concentration-dependent way (Agrawal *et al.*, 2007).

Dendrimers may interact with a wide spectrum of plasma proteins and blood cells when they come

into contact with blood, depending on their physicochemical properties. The stoichiometry of complexation, the molecular hydrodynamic dimensions of the protein in issue, and the occupied protein volume should all be considered in studies analyzing dendrimer plasma protein interactions. Protein structure and functionality, blood cell survival and performance, and dendrimer pharmacokinetics and biodistribution may all be affected by such interaction mechanisms. Recent research has demonstrated that G5 PAMAM dendrimers, regardless of surface functionality (amino, hydroxyl, and carboxylic functionalities), interact with gamma globulins and affect their secondary structure and conformation (Lin *et al.*, 2015).

Conclusion

A significant number of functional groups come together with a relatively tiny molecular size to generate dendrimers, artificial macromolecules with a well-organized structure. Since the development of the first dendrimers, the chemistry of dendrimers has acquired significance. To find out how to create a distinct class of macro and micromolecules and to examine their properties, a project was established. Despite the fact that dendrimers were first identified twenty years ago, the multi-step synthesis is still labor intensive.

In spite of some demerits of dendrimers, the overall merits make it a useful entity for pharmaceuticals. Dendrimers have numerous possibilities due to their flexibility on both a structural and functional level. They could be employed in a variety of fields, including immunology, imaging, photodynamic therapy, pharmacy, biopharmacy, conjugation of oligonucleotides, and the movement of genes and siRNA. As demonstrated in this work, dendrimers that are macromolecular frameworks with an array of advantages that may be changed to ensure targeted and transferable drug delivery. Due to some dendrimers' toxicity, which restricts their application in biomedicine, specific toxicity reduction strategies have been devised.

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