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Recent advances in dendrimer-based drug and gene delivery system

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Abstract
Drug delivery technologies play a pivotal role in optimizing the therapeutic potential of pharmaceutical compounds. Despite the significant advancements, efficient targeted drug delivery remains a complex task. Nano-materials, with their tuneable physicochemical properties, provide a versatile platform for encapsulating and delivering a wide range of therapeutic agents. Among various nano-materials, dendritic nanostructures have appealed focus of researchers for their distinctive structural properties. Dendrimers are well-defined homogenous three-dimensional structures of nano-dimension resembling tree-like branches which have been investigated for combination therapy, where multiple therapeutic agents can be simultaneously delivered, promoting synergistic effects and reducing the development of drug resistance. The advancements in nanotechnology have facilitated the integration of dendrimers with various imaging modalities, enabling theranostic applications that combine drug delivery with real-time monitoring of treatment efficacy. The recent breakthroughs in dendrimer-based drug delivery have demonstrated their potential to revolutionize the pharmaceutical industry by holding promise for personalized medicine, targeted therapy, and improved patient outcomes in the future. However, further studies are been done to address biocompatibility, toxicity concerns, and scalability for successful translation from the laboratory to clinical applications. The study presented here describes the dendrimer's structures and its remarkable properties that open doors to a myriad of possibilities, promising to reshape medicine, technology, and the environment for the betterment of humanity.

Keywords: Dendrimers, drug delivery, drug resistance, nano-materials, targeted therapy

Introduction
Dendrimers have come a long way in the last 25 years since their inception. Originally created as a wonder molecule of chemistry, dendrimer is now in the fourth class of polymers. The word “dendrimer” is derived from a Greek phrase of “dendron”, which means ‘tree or branch like’ and “meros” means ‘part of’ and was chosen due to their structural shape (Vögtle *et al*. 2009) [1]. Between 1979 and 1985, Donald A. Tomalia and his team at Dow Laboratories achieved a significant breakthrough in dendrimer development. They created polymers known as dendrimers, featuring a central core, hollow core, and precise branching tendrils (Abbasi *et al*. 2014) [36]. Over 100 dendritic structures have been discovered since, including polyamidoamine (PAMAM), polypropyleneimine (PPI), and various other dendrimer families based on polyamide, polyether, polyester, and phosphorus (Nath *et al*. 2022) [3]. The initial dendrimer preparation method used a divergent approach, allowing modular construction with exterior modification in the final step. This enables systematic variation of peripheral units, as seen in dendritic box synthesis. Researchers use this method and available dendrimer classes (like DSM poly [Propylene imine] and PAMAM) to create diverse derivatives. Advancements in dendrimer formulations hold promise for new drug, gene products, and combination therapies, expanding the range of nanoscopic applications (Vogtle *et al*. 2009, Abbasi *et al* 2014) [1, 36].
Dendrimers hold immense potential over the other carrier systems, particularly in the field of drug delivery, because of their unique properties. As compared to traditional linear polymers, dendrimers exhibit significantly improved physical and chemical properties (Nath *et al*. 2022) [3].

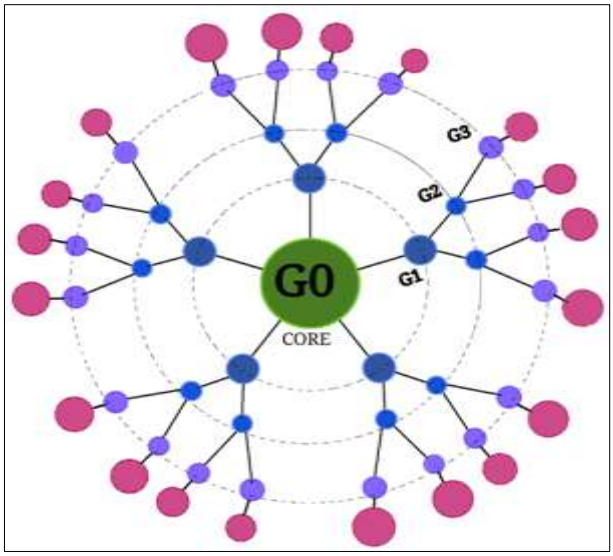

Fig 1: A schematic representation of the Dendrimer Nanostructure

Radially concentric layers in dendrimers are formed by connecting branching units, resulting in higher-generation dendrimers with spherical shapes like G1, G2, etc. as shown in Fig 1.1. Dendrimers, like Poly-L-Lysine, exhibit dense spheroidal properties and are mainly used for polypeptide/protein applications.

Dendrimers are nanoscale drug delivery systems known for their unique properties. These hexametric aggregates have a diameter of approximately 9 nm and a thickness of 2 nm, featuring a spacious central cavity. Ethylene diamine core dendrimers exhibit growth in size from 1.1 to 12.5 nm as they progress from generation 1 to 10 (Madaan *et al*. 2014) [4]. Dendrimers are structured with a central core, dendrons branching out from it, and terminal functional groups, allowing for the attachment of dendrons (Sorokina *et al*. 2022) [5]. These dendritic structures exhibit pharmacokinetic properties, enabling modifications to create various drug delivery systems such as antibody dendrimers, peptide dendrimers, conjugates, or dendritic boxes (Nath *et al*. 2022) [3]. The charged end groups on their periphery facilitate electrostatic interactions with oppositely charged molecules, functioning as polyelectrolytes (Menjoge *et al*. 2010) [6]. Dendrimers possess high solubility in a wide range of solvents, especially organic ones, due to quick dissolution (Nath *et al*. 2022) [3]. Dendrimers are characterized by their high reactivity, allowing precise control of properties through surface functional group modifications, size adjustments, and generation variations (Malkoch *et al*. 2012) [7]. Their solutions have lower viscosity compared to linear polymers, and higher-generation dendrimers exhibit even lower viscosity due to an increased monomer count. Dendrimers with ethylenediamine or ammonia cores and peripheral amino groups offer attachment points for contrast agent conjugation, making them valuable for imaging applications (Xie *et al*. 2022) [8]. Dendrimers exhibit low polydispersity due to their controlled stepwise synthesis, unlike the broad molecular weight distribution seen in linear polymers. Moreover, their unique structural parts, including the core, end-groups, and branched units, allow for self-assembly, with strategies like dendrons recognizing core structures leading to spontaneous dendrimer formation (Zeng *et al*. 1997) [9]. Finally, dendrimers can exhibit biodegradability and biocompatibility, particularly spherical dendrimers with gallic acid shells, which possess strong antioxidant activity, potentially contributing to the treatment of diseases related to oxidative stress (Xie *et al*. 2022) [8].

According to the definition from NNI (National Nanotechnology Initiative) (Wilczewska *et al*. 2012) [10], nanoparticles are small in size of 1 to 100 nm in diameter), have optimised physico-chemical and biological properties that enhance reactive area as well as the ability to cross cell and tissue barrier and are more easily taken up by cells rather than larger molecules, so they can be successfully used as drug delivery tools, making them favourable material for biochemical applications (Ciolkowski *et al*. 2012) [11]. From the pharmaceutical view point it is important that dendrimer–drug complexes or conjugates have already been evaluated in intravenous (Kambhampati *et al*. 2014) [12], oral (Wang *et al*. 2022) [13], transdermal (Chauhan *et al*. 2018) [14], ocular and pulmonary (Wang *et al*. 2022) [13] routes of administration. The potential virtues of dendrimer utilization as drug vehicles include prolonging the residence time of the drug in the circulatory system, protecting the drug from its environment, increasing the stability of the active compound, and tissue targeting.

Dendrimer based drug delivery

Dendrimers as carriers of hydrophobic and hydrophilic drugs

Dendrimers have exhibited remarkable potential in hosting both hydrophobic and hydrophilic drugs, ushering in new possibilities (Lin *et al*. 2010) [15]. For hydrophobic drug delivery, dendrimers establish a protective interior sanctuary that secludes drugs from their aqueous surroundings, shielding them from degradation while augmenting their solubility. Through precise surface functionalization with ligands that discern specific cell receptors or biomolecules, dendrimers can be tailored to target designated tissues or cells, thereby elevating the therapeutic impact of hydrophobic drugs and curtailing their exposure to healthy tissues. Notably, the delicate equilibrium hinges on the Critical Micelle Concentration (CMC)-a critical determinant; a decrease in CMC can provoke dendrimer disintegration and a hasty release of entrapped drugs (Ambade *et al*. 2005) [16]. By incorporating entities like polyethylene glycol (PEG), dendrimer surfaces become hydrophilic, bolstering water solubility and reducing toxicity. Augmenting the surface with amino groups or carboxylic acids further facilitates cell membrane interactions, intensifying cellular uptake. This symbiotic interplay of dendrimer architecture and drug delivery needs is reshaping therapeutic paradigms (Ambade *et al*. 2005, Lin *et al* 2010) [16, 15]. The controlled release of drugs from dendrimers in *in vivo* systems is influenced by dendrimer structure, size, surface chemistry, drug properties, and the biological environment, enabling tailored and sustained drug delivery (Tomalia *et al* 2004) [17]. A study explored drug release from fluorescent dye-conjugated polyamidoamine (PAMAM) dendrimers in mice. These dendrimers, given intravenously, exhibited sustained drug release over days, with a gradual start and accelerated release later on, as observed through fluorescence imaging (Chauhan *et al* 2018) [14].

Dendrimers as carriers of gene

Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus (Chauhan *et al* 2018) [14]. Dendrimers use as

gene delivery vehicles because of their monodispersity, high density of functional groups, well-defined shape and multivalency (Shcharbin *et al*. 2009) [18]. They are able to form condensed polycations under various chemical and physiological conditions with the ability to bind to negatively charged nucleic acid molecules (Klajnert *et al* 2006, Fu *et al*. 2023] [19, 20]. An overall net positive charge of the dendrimer-nucleic acid complex, also called dendriplex, is thereby required to allow binding to the negatively charged cell membrane and thus facilitate cellular uptake (20]. PAMAM dendrimers, prized for their water solubility and modifiable amine groups, are extensively researched for gene delivery, yet higher-generation dendrimers can pose toxicity risks due to their non-biodegradable amide backbones, with sixth-generation dendrimers proving most efficient (Fu *et al* 2023) [20].

Naturally occurring biopolymers in dendrimer designing

While dendrimers are typically synthesized using synthetic methods, there has been growing interest in incorporating naturally occurring biopolymers into dendrimer design. One of the naturally occurring biopolymer that has been used in dendrimer design is hyaluronic acid-based dendrimers which have been developed for drug delivery, imaging, and tissue engineering applications due to their biocompatibility and ability to target specific tissues (Fazal *et al*. 2023) [21]. Other naturally occurring biopolymers that have been explored for dendrimer design include alginate, collagen (Fazal *et al*. 2023) [21], and gelatin. Collagen and gelatin (Kono *et al*. 2012) [22] are proteins found in the extracellular matrix of many tissues in the body and have been used in dendrimer design for tissue engineering and wound healing applications.

Modern insights in the modifications of dendrimers: Hydrogel and Aerogel based dendrimer

Modification of dendrimer surface groups is one of the methods available to obtain compounds characterized by reduced toxicity. Dendrimers having the same backbone but different terminal groups, such as hydroxyl and carboxyl groups, exhibit much lower cytotoxicity. Hydrogels possess great potential in bio-fabrication because they allow cell encapsulation and proliferation in a highly hydrated three-dimensional environment, and they provide biologically relevant chemical and physical signals (Bi *et al*. 2015) [23]. Hydrophilic gel networks based on dendritic macromolecules have been evaluated as medium-sensitive matrices and as promising delivery systems (Du *et al*. 2015) [24]. PAMAM dendrimer hydrogels combine the properties of PEG hydrogels and dendrimers, offering versatile applications in tissue engineering and drug delivery.

PAMAM dendrimer hydrogel networks possess the exceptional ability to concurrently deliver hydrophobic and hydrophilic drugs, making them a promising platform for precise modulation of cell-scaffold interactions in tissue engineering (García-González *et al* 2021) [25].

Aerogels

Aerogels are created by substituting the liquid in a gel with a gas, sharing similarities with biomedically used hydrogels, both comprised of 3D networks. However, the key distinction lies in the significantly higher degree of swelling exhibited by dried aerogel networks (Nita *et al*. 2020) [26]. Freeze-drying is intended to keep the original swelling achieved by the hydrogel in a favourable aqueous medium through rapid freezing of water inside the pores followed by sublimation under low pressure conditions (García-González *et al* 2021) [25].

Biological/Immunological challenges

Despite the benefits of dendrimers as drug delivery carriers, some challenges remain to be solved. The size and surface chemistry of dendrimers are closely related to their toxicity and biodistribution (Kannan *et al*. 2014) [27]. Dendrimer toxicity in biological system is generally characterized by haemolytic toxicity, cytotoxicity and haematological toxicity (Jain *et al* 2010) [28]. Dendrimers, as biocompatible nanoparticle macromolecules, are used for their unique properties as carriers of other molecular structures, in order to improve the activity and efficiency of an active drug molecule and also to reduce its toxicity (Chauhan *et al*. 2018) [14]. It has been shown that the cytotoxicity of the dendrimer depends on the generation to which it belongs and also on the nature of its surface, given by terminal functional groups. Cytotoxicity was highlighted in cationic, amine dendrimers. Studies also showed a correlation between cytotoxicity and dendrimer generation (Abd-El-Aziz *et al*. 2018, Tomalia *et al*. 2003) [29, 30]. Glycodendrimers are a newer type of dendrimers, these modulations leading to a significant decrease in cytotoxicity (Augustus *et al*. 2017) [32].

Future prospects and Conclusion

Dendrimers, with their highly controlled and branched structure, serve as versatile platforms for drug delivery. They can be functionalized with various groups for targeting, drug encapsulation, or imaging, making them ideal for precise and effective therapeutic applications. Dendrimers are promising in gene therapy by delivering nucleic acids (Kaurav *et al*. 2023) [33], offering tailored drug release, targeting, and pharmacokinetics. They find utility in diverse therapeutic areas, including antimicrobial, anticancer, and vaccine development, owing to their unique properties like multivalency and high surface area (Filipczak *et al*. 2021) [24]. Additionally, dendrimers can be harnessed to play a role in experimental approaches like boron neutron capture therapy (BNCT) by facilitating the directed delivery of therapeutic agents (Wolinsky 2008) [35].

Conflict of Interest

The authors have no potential conflict of interest.

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