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Dendrimers: An Innovative Tool of Drug Delivery System

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Abstract: About 40% of newly developed drugs are rejected by the pharmaceutical industry due to poor bioavailability, low water solubility and cell membrane permeability. New delivery technologies, such as uniformly sized and well-defined nanostructures, are of interest in biomedical applications due to their ability to cross cell membranes and reduce premature clearance risk. Dendrimers are three-dimensional hyperbranched nanoparticles that are employed in drug delivery to enable the loading of active molecules onto their surface. They enhance biological qualities, bioavailability, and solubility. During synthesis, dendrimers can be altered to improve their biocompatibility and ability to target ligands. They could be used as gene or medication carriers. Drug distribution in clinics can benefit from the special properties of dendrimer-based delivery systems. Dendrimers can be loaded with a variety of therapeutic compounds through chemical or physical interactions, including big nucleic acid molecules and small hydrophobic or hydrophilic molecules. Multiple treatment options with exceptional efficacy are made possible by dendrimer-based delivery systems improved medication solubility and cellular permeability.

Keywords: Dendrimers, Hyperbranched nanoparticles, Drug delivery system, Therapeutic

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Introduction

The pharmaceutical industry rejects about 40% of newly created medications because they have inadequate bioavailability due to low water solubility and low permeability, which means they will not help in the patient recovery. This difficulty might be solved with the use of new delivery technologies. Nanostructures possessing consistent and well-defined particle size and shape are highly desirable for biomedical applications due to their capacity to penetrate cell membranes and minimize the risk of premature body clearance. Dendrimers are the perfect carriers in these applications because of the high degree of control over the dendritic architecture includes size, branching density, and surface functionality etc. (Sonke, 2004; Svenson and

Tomalia, 2005). Dendrimers are highly branched polymeric macromolecules with specific and consistent sizes and forms. Their basic framework includes three major components: a central core, repeated branching units, and terminal groups that give variable surface features. They have potential as systems for drug and gene delivery applications because of the great degree of control that can be achieved over their architecture (Liu and Frechet, 1999).

History of dendrimers:

The Greek word "dendron" (meaning tree, meros, or branch) is where the name "dendrimer" originates. The first "cascade" and "nonskid-chain-like" molecules with molecular cavity topologies were created and described by Buhleir and associates as early as 1978 (Vogtle *et al.*, 2009). These molecules were subsequently identified as the earliest examples of dendritic polymers. Tomalia *et al.* (1985) termed dendrimers which are polymers with a central, hollow core and tendrils that branched outward, one from another, in an exact, predictable fashion. The early history of dendrimers was influenced by these two research groups. More than 100 dendritic structures have been described thus far, with some of the most well-known dendritic families including polyamide, polyether, polyester, and phosphorus-based dendrimers, as well as poly-amidoamine (PAMAM) and polypropylene-imine (PPI) dendrimers (Liko *et al.*, 2016).

Structure and Morphology:

Dendrimer molecules have a core, which is an atom or collection of atoms in the centre of the molecule. Through a number of chemical processes, the branches of additional atoms known as "dendrons" emerge from this central structure. The precise structure of dendrimers remains an area of contention, namely about whether the end-groups fold back into a densely packed core or whether the dendrimers are fully stretched with maximum density at the surface (Zimmerman, 1997; Zeng and Zimmerman, 1997). With dendrimers, a degree of controllability not possible with most linear polymers can be achieved, resulting in macromolecules that are almost spherical and virtually monodisperse, with several peripheral groups.

Like other specialized scientific domains, dendrimer chemistry has its own nomenclature and terminology. Moreover, a condensed structural nomenclature is utilized to depict the many chemical reactions occurring at the dendrimer surface. Similar to dendrimers, dendrigrafts are a kind of dendritic polymers that can be built with a clearly defined molecular structure, or being monodisperse (Tomalia *et al.*, 1991). Dendrimers' unique structure offers exceptional prospects for host-guest interaction (Fig. 1), and it is particularly well-suited to participate in multivalent interactions. Simultaneously, dendrimers were initially suggested for use as container compounds, in which tiny substrates are confined inside the dendrimer's internal spaces (Maciejewski, 1982). Many years ago, it was demonstrated through experiments that unimolecular micelle characteristics may be found in dendrimers and hyperbranched polymers (Kim and Webster, 1990).

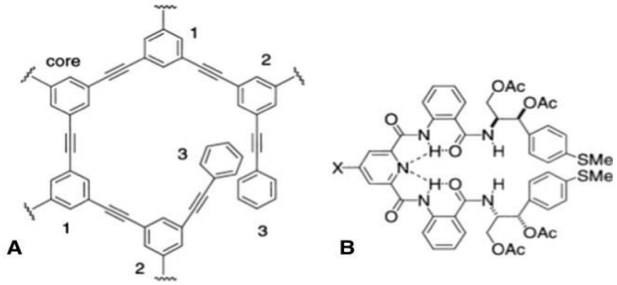

Fig. 1: Structural morphology of dendrimer.

Types of dendrimers:

- More type dendrimers consist of phenyl acetylene subunits at the third-generation different arms may dwell in the same space, and the fourth-generation layer potential overlaps with the second-generation layer.
- Parquette-type dendrons are chiral, non-racemic, and with intramolecular folding driven by hydrogen bonding. The various parts

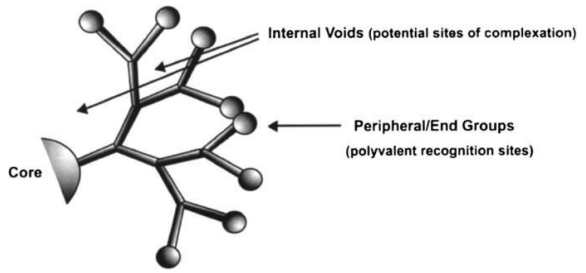

Fig. 2: Main parts of a dendrimer.

of dendrimers is shown in Figure 2.

(1) *Simple Dendrimers*: They have simple monomer units. The convergent synthesis of a sequence of monodisperse are lester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 and 46 benzene rings linked symmetrically and have molecular diameters of 45 A.

(2) *Liquid crystalline dendrimers*: Mesogenic monomers, such as mesogen functionalized carbosilane dendrimer, are used to create liquid crystalline dendrimers. Functionalization of the carbosilane dendrimers' end group results in liquid crystalline dendrimers that form a wide smectic phase between 17°C and 130°C. These dendrimers have 36 mesogenic units that can be joined by a C-5 spacer.

(3) *Chiral Dendrimers*: Chiral dendrimers, such as those derived from pentaerythritol, are formed by connecting four chemically similar branches to a central achiral core.

(4) *Micellar Dendrimers*: These dendrimers have a unimolecular micelle configuration. Water soluble dendrimers are composed of aromatic polymeric chains that provide an environment similar to *micellar structures. They form complexes with small organic molecules in water.*

(5) *Hybrid* Dendrimers: Dendritic and linear polymers are prepared as hybrid block or graft copolymers. Hybrid dendritic linear polymers provide potential as surface active agents, compatibilizers, or adhesives.

(6) *Amphiphilic Dendrimers*: These spherical dendrimers exhibit asymmetrical but regulated chain end chemistry. These can be directed at the interface to create liquid membranes that neutralize aqueous organic emulsions (Shinde *et al.*, 2010).

Synthesis:

Cascade Reactions:

Chemists were aware of the fundamental cascade or repetitive procedures that are used today for synthesis considerably earlier. Solid-phase peptide synthesis, for instance, is based on comparable concepts. Conversely, biology has long made use of comparable iterative techniques in biochemical synthetic pathways; fatty acid production serves as one illustration (Tomalia, 1995).

Dendrimers can also be produced using two other methods:

The divergent technique, which originated in the early times, begins with the core of the dendrimer, to which the arms are joined, and progresses through an extensive and step-by-step process of adding building blocks. This involves synthesis of radially symmetric poly-amidoamine (PAMAM) dendrimers using ammonia as the trivalent core; the generations are added at each synthetic cycle (two steps), leading to an exponential increase in the number of surface functional groups (Grayson and Frechet, 2001). Whereas in the convergent technique, synthesis begins on the outside, with the chemical structure that eventually becomes the outermost arm of the final dendrimer. In this technique, the eventual generation number is predetermined, forcing the synthesis of branches of a variety of required sizes prior for each generation (Tomalia *et al.*, 1986). Synthesis of dendrons or wedges or branches that will become the periphery of the dendrimer when coupled to a multivalent core in the last step of the synthesis (Mehra *et al.*, 2015). The cascade reaction sequence and production of dendrimers are shown in Figures 4 and 5.

Applications of Dendrimers:

- *Biomedical field*:

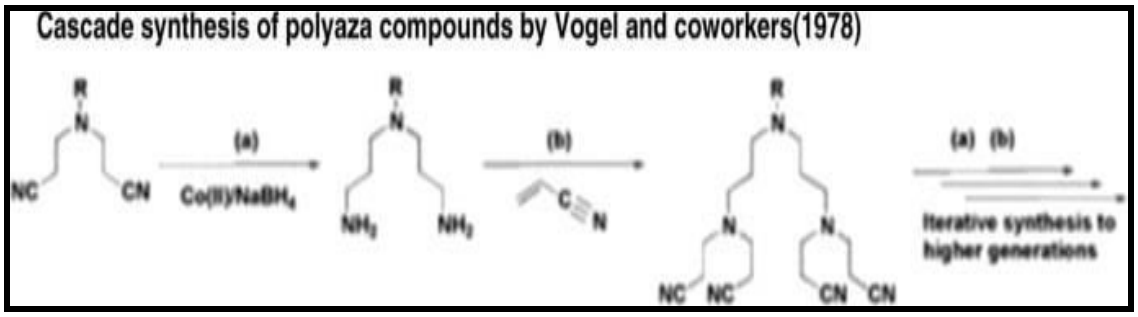

Fig. 3: Cascade reaction sequences.

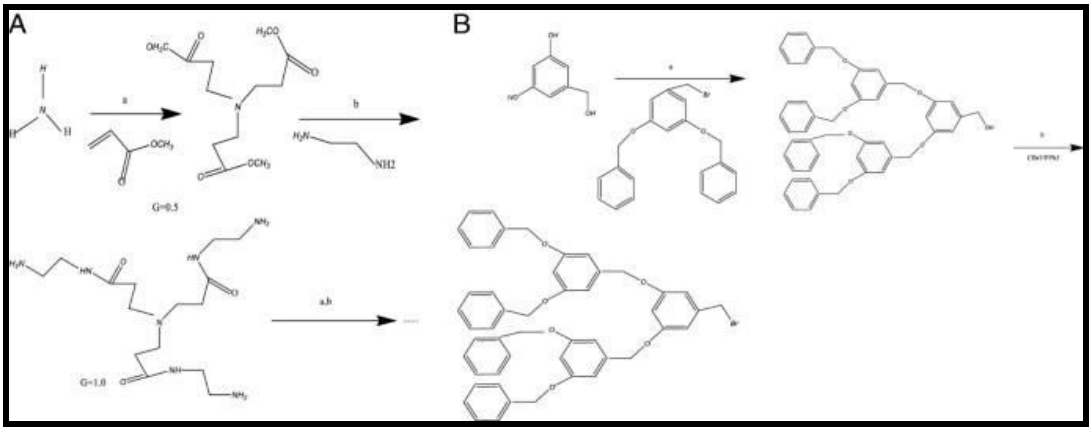

Fig. 4: Illustration of dendrimers production.

These dendritic polymers are readily functionalized and exhibit similarities to viruses, proteins, and enzymes. Dendrimers and other molecules have two possible internal void encapsulations: attachment to the periphery and encapsulation (Jain and Asthana, 2007). Many forms of this substance are used in modern medicine as possible blood substitutes, such as poly-amidoamine dendrimers (Kukowska-Latallo *et al*., 2005).

- *Routes of drug delivery*:

Materials at the nanoscale offer special qualities such high purity, high drug payload, good colloidal, targeting potential, shelf stability, structural homogeneity, and effective membrane transport. PAMAM dendrimers, for example, have carried the antitumor drug methotrexate and fluorescein for tracking. Because of these special features, dendrimers are one of the talented technologies of recent times and have served as an exceptional platform to reach the development as new drug delivery scaffolds (Yiyun *et al*., 2007; Tolia and Choi, 2008).

- *Ocular drug delivery*:

Due to their adaptable structure, precise size, and possibly advantageous ocular biodistribution, dendrimers have received a great deal of interest as ocular drug delivery methods (Svenson and Tomalia, 2012). It has been shown that surface-modified PAMAM dendrimers with carboxylic or hydroxyl surface groups increase residence time and improve pilocarpine absorption in the eye **(**Malik *et al.*, 1999). When dendrimers are combined with polyethylene glycol (PEG), hydrogels are produced that can be used to seal eye injuries and produce cartilage tissue (Vandamme and Brobeck, 2005).

- *Transdermal drug delivery*:

It has been established that dendrimers are efficient transdermal drug delivery methods for antibacterial, antiviral, antitumor, and

nonsteroidal anti-inflammatory medicines (NSAIDs). PAMAM dendrimers have been demonstrated earlier (Desai and Yang, 2008) and other researchers to significantly boost the transdermal transport of diflunisal and ketoprofen, two model NSAIDs (Balzani *et al.*, 2000; Kandekar *et al.*, 2011). When cisplatin, an anticancer medication based on platinum, was encapsulated into PAMAM dendrimers, the resultant conjugates showed reduced toxicity, slower release, and greater accumulation in solid tumors in comparison to the drug (Mostafavi and Ataie, 2015).

- *Targeted drug delivery*:

Targeted medication delivery is a method of administering a therapeutic chemical in a site-specific way to a certain cell type or tissue. One type of vehicle under consideration for use in targeted medication delivery is the dendrimer. Compared to systemic distribution, targeted delivery of chemotherapy drugs to tumor cells reduced side effects (Mostafavi and Ataie, 2015). The production of generation 5 PAMAM dendrimers coupled with folic acid for methotrexate targeted distribution was described.

- *Photodynamic therapy*:

Photodynamics (PDT) is an excellent method for treating some types of cancer. More than 30 years ago, PDT was intended to be a useful cancer therapy, but it has limitations. Photosensitizers are primarily responsible for PDT's effectiveness, and efforts to develop a more potent second generation are ongoing. PDT is a promising therapeutic approach that uses a mix of light and photosensitizers to kill sick cells and tissues by releasing reactive oxygen species. Dendrimers are an interesting candidate for more research because of their architecture, which is suitable for integrating specific functional moieties (Mostafavi and Ataie, 2015).

- *Magnetic resonance imaging* (*MRI*):

Dendrimers have recently been investigated as a potential new class of macromolecular MRI contrast agents. Gadolinium-based contrast agents are the most often utilized MRI contrast agents (Mostafavi *et al.*, 2015). Several research groups have reported on the covalent attachment of Gd (III) complexes to PAMAM dendrimers to create distinct macromolecular contrast agents for MRI. Gd-diethylenetriamine penta acetic acid (DTPA)-loaded completely PEGylated PAMAM dendrimers have been produced.

Enhancing solubility:

It is anticipated that PAMAM dendrimers will be useful in improving the solubility of medication delivery systems. Dendrimers are unimolecular micelles because of their hydrophilic interiors and exteriors. Dendrimer-based carriers have a chance to improve the oral bioavailability of therapeutics that cause issues. Consequently, dendrimer nano carriers present a chance to improve the bioavailability of poorly soluble medications and/or efflux transporter substrates (Mostafavi *et al.*, 2015).

- *Dendritic sensors*:

Despite being single molecules, dendrimers can have a large number of functional groups on their surface. This makes them attractive for purposes where a high number of species must be in close contact or have a covalent link. A fourth-generation poly (propylene amine) dendrimer adorned with 32 dansyl units at the perimeter was the subject of an investigation by Balzani and colleagues (Froehling, 2001). Appropriate metal ions can coordinate since the dendrimer's inside contains thirty aliphatic amine units. The intense fluorescence of every dansyl unit was found to be muted with the incorporation of a Co^{2+} ion into the dendrimer. A dendrimer concentration of 4.6×10^{-6} M can be used to detect low amounts of Co^{2+} ions (4.6×10^{-7} M).

- *Anticancer drugs*:

The characteristics of drugs conjugated with polymers include a longer half-life, increased stability, solubility in water, reduced immunogenicity, and reduced antigenicity (Froehling, 2001). Tumors with certain

pathophysiological characteristics, such as hypervascularization brought on by extensive angiogenesis, heightened permeability of the tumor vasculature, and restricted lymphatic drainage, allow for passive targeting and the selective accumulation of macromolecules in the tumor tissue. "Enhanced permeation and retention" (EPR) is the term used to describe this phenomena (Froehling, 2001). The drug-dendrimer conjugates exhibit selective accumulation in solid tumors, low systemic toxicity, and good solubility. Various approaches, including as encapsulation, complexation, or conjugation, have been suggested to enclose medicinal molecules, genetic materials, targeting agents, and colors within the dendrimer structure.

Conclusion

Dendrimer drug delivery systems are gaining a lot of attention as a useful way to transfer bioactive substances like genes and pharmaceuticals. They offer a venue for the medication or gene attachment and release via a variety of pathways. A brief overview of the role of dendrimers in biomedical applications and improved drug delivery is given. Dendrimers, which combine a condensed molecular structure with a large number of functional groups, are referred to as highly defined artificial macromolecules. One of the key elements in the effective use of dendrimers is their pharmacokinetic characteristics. Over the past thirty years, many uses for dendrimers have been investigated. The advent of well-controlled dendrimer structures with several surface groups, which may be used to display a variety of biological molecules such peptides, proteins, sugars, and targeting agents, is the result of advancements in regulated polymerization and synthesis processes.

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