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Dendrimers in Medicine: Properties, Drug Encapsulation Mechanisms and Applications

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Abstract

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure that has a typically symmetric core, an inner shell, and an outer shell. Each group of dendrimers is very similar in terms of size, shape, length of branches, surface functional groups, and surface properties. Dendrimers can trap different molecules among their branches according to their size, surface properties (such as electrical charge), and functional groups, and prevent them from being affected by external factors. They can also release the molecules inside them according to environmental conditions. Dendrimers can be used to transport hydrophobic molecules in a hydrophilic environment and vice versa. These varied characteristics make dendrimers a good choice in the medical field, and this review covers their diverse applications.

Keywords: Polymeric, Drug delivery, Dendrimers, Medical, Pharmaceutical, Physicochemical

Introduction

Dendrimers are mostly symmetrical about their center. Another group of similar chemical compounds that are tree-like also have symmetry about a focal point [1-5]. Dendrimers are 0-dimensional branched molecules in nanoscale that consist of a central core from which many branches branch out step by step and in a repetitive manner similar to the branches of a tree. Each group of dendrimers is very similar in terms of size, shape, length of branches, surface functional groups, and surface properties [6-10]. Dendrimers can trap different molecules among their branches according to their size, surface properties (such as electrical charge), and functional groups, and prevent them from being affected by external factors [11-14]. They can also release the molecules inside them according to environmental conditions. Dendrimers can be used to transport hydrophobic molecules in a hydrophilic environment and vice versa [15-19]. In view of the above, dendrimers play an important role in the targeted transport and delivery of drugs. They can attach, transport and finally release various molecules to their surface due to the numerous functional groups on their surface, which can also be used to target drug delivery to a specific area of the body [20-25]. Although the origin of dendrimers can be considered linear polymers and then branched polymers, the amazing structural properties of dendrimers and highly branched macromolecules are completely different from those of traditional polymers [26-31]. Despite the use of polymers in drug delivery systems, dendrimers have more advantages compared to them. They have limited dispersion and dimensions in the nanometer range, which makes it easier to pass through biological barriers [32-37]. Dendrimers can encapsulate guest molecules via receptors on their surface or within the cavities between the branches [38-40]. The unique properties of dendrimers, such as controlled size, Mono dispersity, and variable surface groups, make them desirable for biomedical applications [41-45]. The end groups in dendrimers can be functionalized with various therapeutic and imaging agents in a specific and controlled manner, which has the potential for their use in targeted drug delivery [46-50]. In addition, the presence of empty cavities in dendrimers is used to

encapsulate hydrophobic drug molecules [51-53]. The presence of tertiary amine groups in Poly amidoamine dendrimers induces acid-base interactions and hydrogen bonds, as well as noncovalent interactions with encapsulated host molecules [54-57]. All these features make dendrimers suitable agents for the solubilization of hydrophobic drugs [58-61]. The emergence of polyethylene glycol-functionalized dendrimers, which are larger dendrimers, increases solubility in water and increases drug loading. Dendrimers are used in various fields: Pharmacology and drug delivery, synthesis of nanoparticles, sensors, gene delivery, blood exchange. With the increasing progress of nano pharmaceuticals, we are witnessing the use of dendrimers as suitable carriers for drugs [62-67]. The tight spherical shape of dendrimers, a class of 3-dimensional, nanoscale polymers, is what distinguishes them in solution (**Figure 1**). Although dendrimer research started in the 1990s, Tomalia *et al.* did not find the first family of high-branched polymers until 1931 [1-4]. The term dendrimers, which comes from the Greek word dendron, which means tree, was used to describe these extremely branching molecules [68-72]. Another group discovered these polymers at the same time and named them arborols, which is Latin for tree [73-78,221-224]. The remarkable structural characteristics of dendrimers and high-branched macromolecules differ greatly from those of conventional polymers, despite the fact that dendrimers may be regarded of as linear polymers that eventually became branched polymers [79-82,225-228]. Dendrimers provide greater advantages than polymers, even though they are used in drug delivery systems [83-87,229-231]. Their nanoscale size and modest polydispersity facilitate their passage across biological barriers [88-92,232-235]. Dendrimers have the ability to trap guest molecules in cavities between branches or transport them through receptors on their surface [93-97,236-240]. For biological applications including gene transfer, imaging materials, and the delivery of active medications, the creation of molecular nanostructures with the right particle size and shape has been taken into consideration [98-101,241-243]. The medicine can be delivered via dendrimer carriers via the skin, eyes, mouth, and lungs, among other linkages [102-105,244-245].

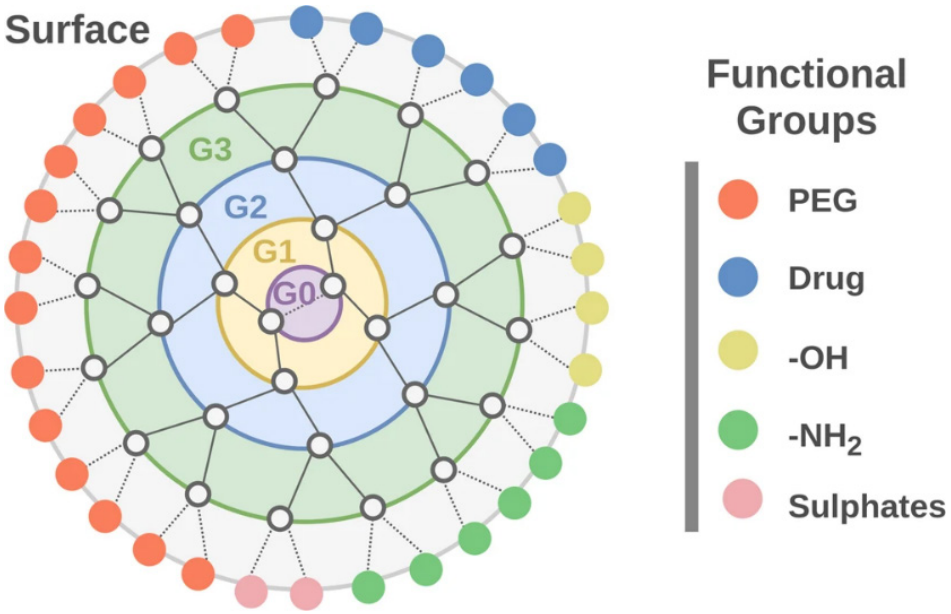


Figure 1 Monomeric units are layered one after the other around a central core (G0) in the fundamental structure of a dendrimer. Any monomeric unit can form a dendrimer as long as it has 2 or more functional groups that can be used to create new generations. Circles are used to represent surface functional groupings [252].

He *et al.* [304] reported a mannose conjugated PAMAM dendrimer for the targeted delivery of liver-x-receptor (LXR) ligands to macrophages as mannose can bind specifically to mannose reporter expressed on macrophage surface.

Pryor *et al*. [305]. studied the toxicity of PAMAM on embryonic zebrafish models and found that cationic PAMAM generation 6 was statistically more toxic than both neutral PAMAM generation 6 and anionic PAMAM generation 6 at the same concentration.

Method of preparation of dendrimer

Novel dendrimer structures were quickly synthesized using this technique (Click Chemistry). The strategy aims to create environmentally friendly, carbon-rich dendrimers. The most common processes for creating dendrimers are thiol-ene click reaction (TEC), thiol-yne click reaction (TYC), and copper-assisted azide-alkyne cycloaddition (CuAAC) [106-110]. These click reactions attracted a lot of interest because of their quantitative synthesis yields, low reaction conditions, and coupling specificity [111-116]. The branching units are expanded and linked to additional groupings. In order to produce a full dendrimer, developing branches are joined to a core when they reach a certain size (**Figure 2**) [178]. Compared to divergent synthesis, convergent synthesis has several benefits (a). Because there is less chance of side reactions, it makes it possible to better regulate dendrimer structure by increasing the likelihood of functional groups rising throughout the dendrimer's structure and forming symmetric, well-defined dendrimers [117-122]. (b). With this approach, less chemicals are used. (c). Because purification is simple following each synthesis step, this approach yields purer compounds [123-126]. Despite the benefits listed, there are a number of issues with this approach; (a) Dendrimer surface functionalization is extremely challenging, and (b) the steric barrier shown in high generation dendrimers may be a challenge in their manufacture [127-132]. Dendrimers are classified according to their interior cavities, terminal functional groups, and form (**Table 1**).

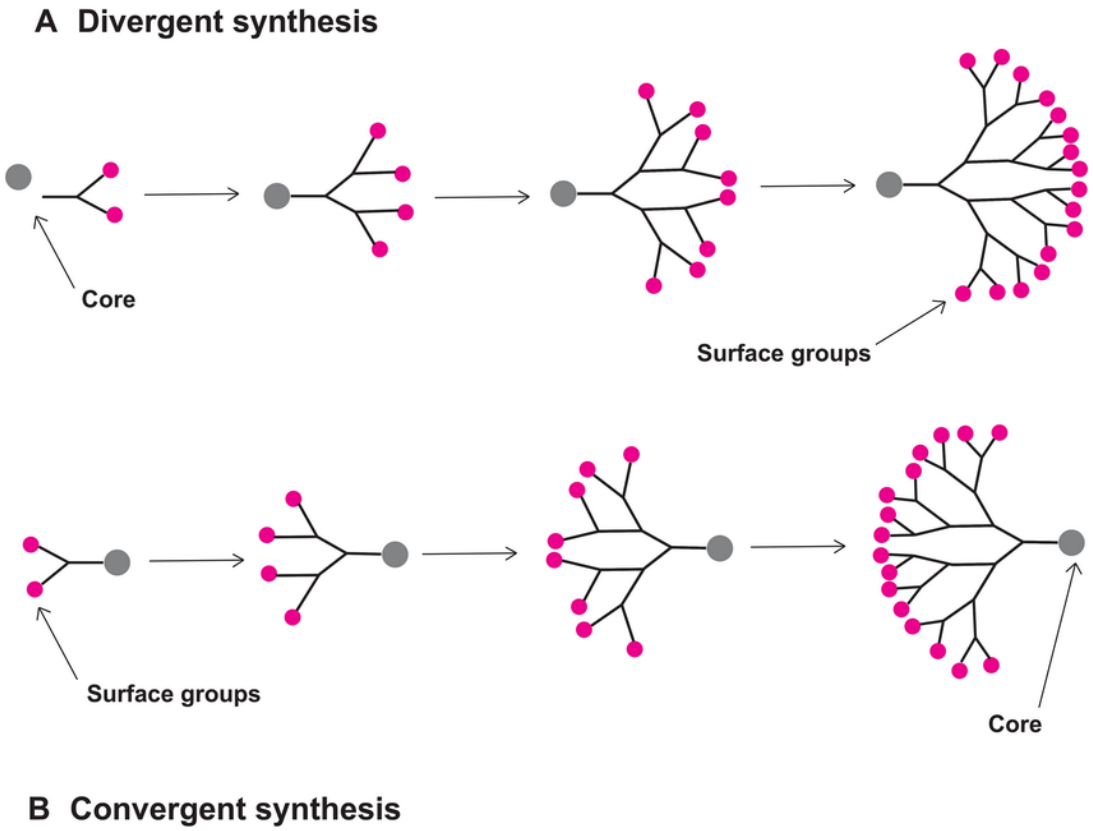


Figure 2 Synthesis dendrimers by (A) Divergent method, (B) Convergent method [178].

Table 1 Types of dendrimers.

Type of dendrimer	Synthesis	Identification
Polypropylene imine (PPI) dendrimer	Divergent	[185-186]
Polyamidoamine (PAMAM) dendrimer	Divergent	[187-189]
Frechet-type dendrimer	Convergen	[190]
Core-shel tecto dendrimer	Divergent	[191]
Chiral dendrimer	Convergen	[192]
Liquid crystalline dendrimer	Convergen	[193]
Peptide dendrimer	Convergen	[194,195]
Multiple antigen peptide dendrimer	Divergent and convergent	[196]
Glycodendrimer	Divergent and convergent	[197]
Hybrid dendrimer	Divergent	[198]
Polyester dendrimer	Divergent	[199,200]

Features of dendrimers

Dendrimers are either very poorly defined or have a restricted structural variety as compared to other nanoscale synthetic structures (such as carbon nanotubes, buck balls, or conventional polymers) [133-136,246-248]. The characteristics of the surface groups have a significant impact on the solubility of dendrimers [64-66]. For instance, dendrimers become soluble in polar solvents when hydrophilic groups are present, while they become more soluble in non-polar solvents when hydrophobic end groups are present [137-142,249-251]. Although there are many compounds with potent therapeutic qualities, they are not employed for medicinal reasons due to their insoluble nature [143-147]. Water-soluble dendrimers have the ability to attach to hydrophobic compounds that have antibacterial or antifungal qualities [148-151]. These complexes are regarded as drug delivery systems because of the potential for the bound drug to be released upon interaction with the target species [152-157]. Dendrimers are perfect for biological applications because of their special qualities, which include changeable surface groups, monodispersed, and regulated size [158-161]. Targeted delivery may be possible since different therapeutic and imaging agents can functionalize the end groups in dendrimers in a particular and regulated way [162-166]. Hydrophobic medicinal molecules are also encapsulated in dendrimers' unfilled holes. Because type III amine groups create non-covalent interactions with the enclosed host molecules, they form hydrogen bonding and acid-base interactions in polyamidoamine dendrimers (PAMAM = Polyamidoamine) [167-172]. The advent of bigger dendrimers functionalized with polyethylene glycol (PEG) results in improved drug loading and water solubility [173-176]. Ibuprofen has been encapsulated and their absorption into cells monitored using amine-functionalized "PAMAM" dendrimers of generation G3 and G4 [73-78].

Types of dendrimers

Due to their symmetrical forms, single scattering, and branching structure, several dendrimers with distinct functionalities have been synthesized in recent years for use in laboratory and experimental study. These are a few dendrimers with various characteristics [79,80].

Liquid crystal dendrimers

Mesogenic monomers, or liquid crystals, like mesogenic carboxylane dendrimers, are examples of these dendrimers. Sin Namville groups were used to create the first liquid crystal dendrimer [177-180]. They can deliver targeted medications because of their E-Z isomerization characteristics. Liquid crystal dendrimers [81,82] are seen in **Figure 3**.

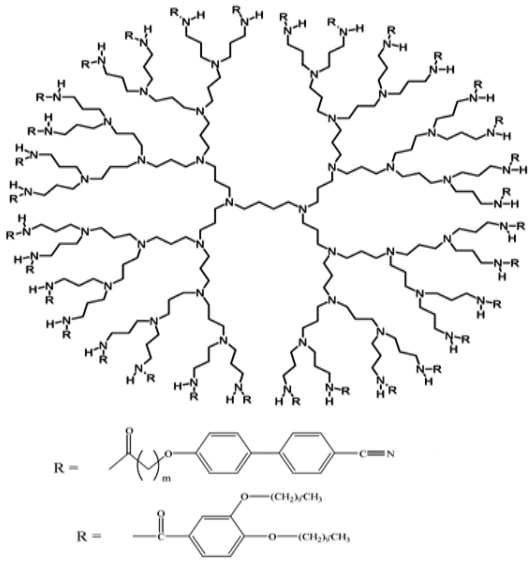


Figure 3 Liquid crystal dendrimers [179].

Tecto-dendrimers

A core dendrimer encircled by surrounding dendrimers makes up tecto-dendrimers. The PAMAM dendrimer's single-shell core is seen in **Figure 4**. The Michigan Institute of Nanotechnology has developed tecto-dendrimers for biological and therapeutic applications that may be used for drug administration, disease site diagnostics, patient cell detection, treatment effectiveness, and status reporting [181-185].

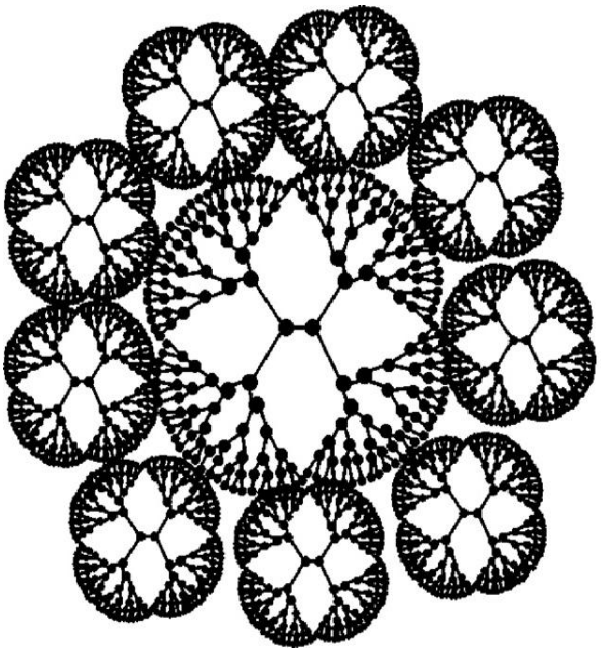


Figure 4 Core-shell PAMAM Tecto-dendrimers [180].

Chiral dendrimers

The existence of branches that are architecturally entirely distinct but chemically identical (chiral species) is what causes chirality in dendrimers [186-190]. Chiral dendrimers are also useful for targeted medication release and chiral component detection in the body

because of the variations that may be employed despite the presence of chiral compounds in these species. Chiral dendrimers [1-4,28-30] are shown in **Figure 5**.

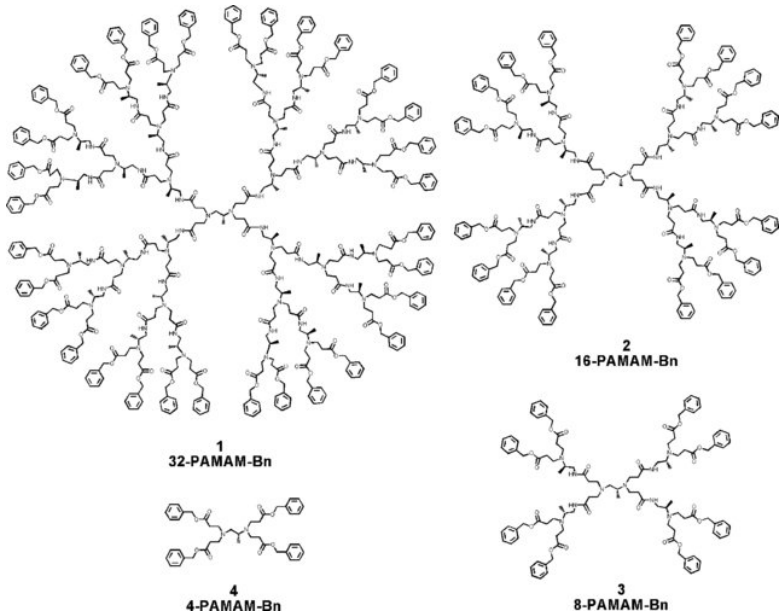
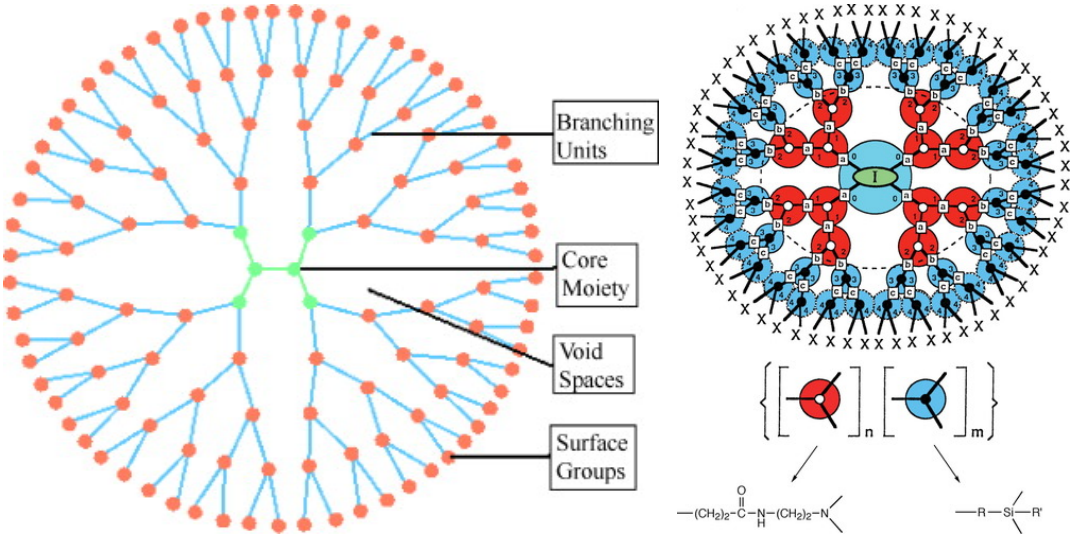


Figure 5 Chiral PAMAM dendrimer (1) - (4) series structure [181].

PAMAMOS dendrimers

Poly (amidoamine-organosilicon) dendrimers that are organized radially (PAMAMOS = poly (amidoamine-organosilicon)) form single-molecule micelles with an organosilicon (OS) on the exterior and nucleophilic polyamidoamine (PAMAM) within. A PAMAMOS dendrimer [191-195] is depicted in **Figure 6**.



(a) (b)

Figure 6 (a) PAMAMOS dendrimers [182] and (b) Generalized illustration of the dendrimer structure of PAMAMOS. Blue: External OS branch cells; red: Inside PAMAM branch cells. I stands for the core atom or atomic group; X for inert or reactive end-groups; generations are indicated by the numerals 1, 2, 3, 4, …; PAMAM-PAMAM, PAMAM-OS, and OS-OS chemical bonds are represented by the letters a, b, and c, respectively [184].

Hybrid dendrimers

Dendritic and linear polymers combined in hybrid components or joined copolymer forms are known as hybrid dendrimers [196-200]. Hybrid dendrimers [1-4] are seen in **Figure 7**.

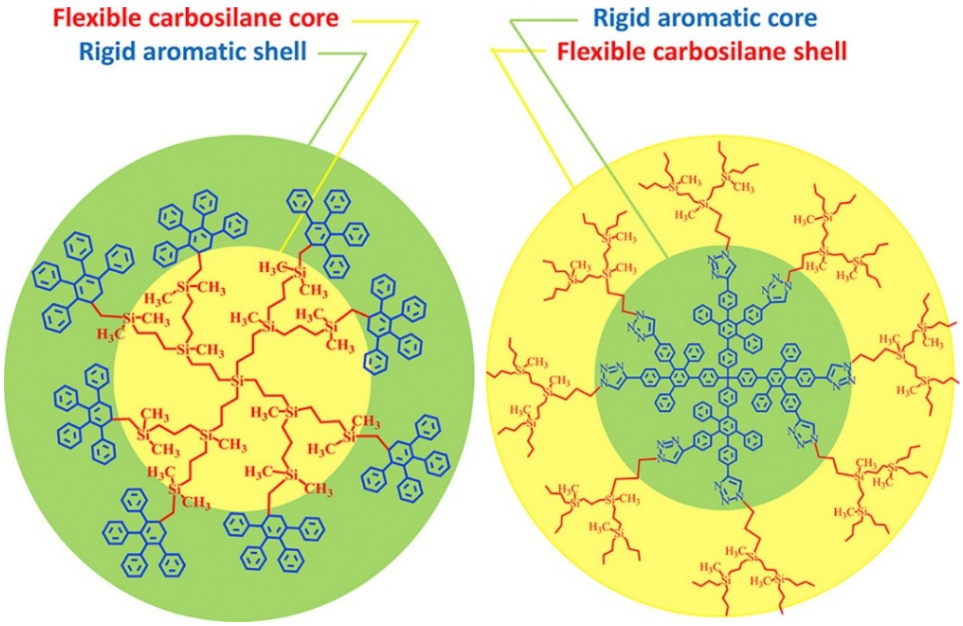


Figure 7 Hybrid dendrimers [183].

Peptide dendrimers

Peptide dendrimers are those that have peptides on their body surface, as opposed to regular dendrimers and dendrimers that include amino acids. These peptides may be found in nucleus or branching units [201-204]. Peptide dendrimers are essential in several areas, including cancer, antibacterial, antiviral, central nervous system, anesthetic, asthma, allergy, and calcium metabolism, because of their biological and therapeutic qualities [205-210]. Peptides are highly helpful for medication delivery because they are absorbed into the cell [211-214]. Peptide dendrimers are shown in **Figure 8**.

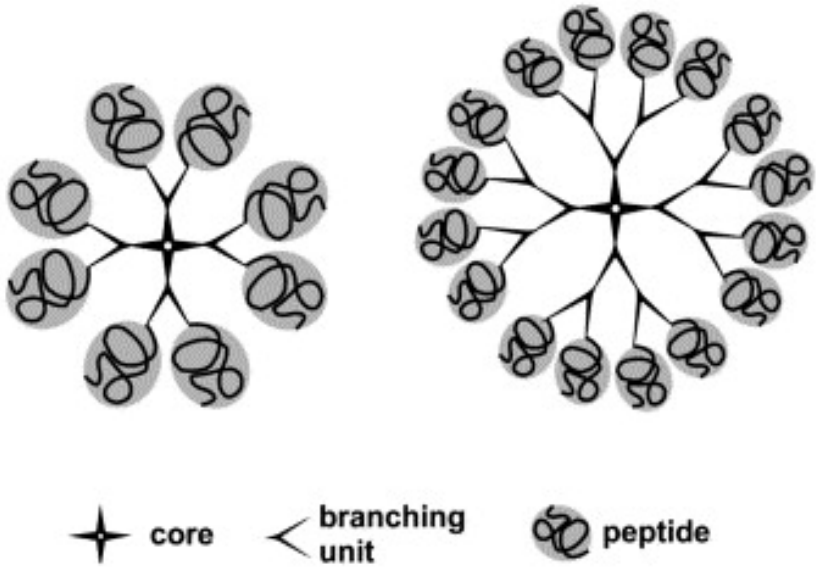


Figure 8 Peptide dendrimers [1].

Glycodendrimers

The promise of glycodendrimers as multivalent probes for glycobiology has undoubtedly been the main factor behind the development of techniques for their manufacture and investigation [215-218]. As a result, the majority of scientists working in this sector have looked for biological uses for the amazing compounds they have created. We shouldn't discount the possibility of glycodendrimers as innovative and useful materials, nevertheless, as the promise of polymers with unique characteristics in the context of a material generally motivated the early development of dendrimers [219-224]. In this context, the authors' group created unique discotic liquid crystals called glucosyl–TRIS dendrimers based on triphenylene cores (**Figure 9**). Since both of these molecules are known to produce liquid crystalline columnar mesophases, they may be thought of as a "constitutional marriage" between traditional thermotropic discotic molecules based on n-alkoxytriphenylene derivatives and amphiphiles based on carbohydrates. As a result, 2 first-generation dendrimers were created using a traditional convergent method, each with a different number of methylene units (5 and 10) in the spacers between the dendrons and cores [225-229]. This design can be interpreted as either the addition of a "functional" core, which has the ability to self-assemble into columnar stacks, to a glycodendrimer or as the addition of glycodendron groups to previously identified liquid crystalline materials, which could change the properties of the materials. The characteristics of the 2 dendrimers in **Figure 9** are radically different. The compound with a longer 10-carbon linker between the core and glycodendrimer end groups forms hexagonal columnar stacks that give rise to a fluid birefringent texture between 165 and 220 °C, which can be seen by polarizing microscopy [230-235]. In contrast, the compound with only 5 methylene units in the linkers exhibits no mesomorphic behavior under an optical polarizing microscope and an X-ray diffusion pattern consistent with an amorphous solid. The comparatively large glycodendrons in this instance do not interfere with the triphenylene units' capacity to form columnar stacks, as evidenced by the strong peak in the powder X-ray study that corresponds to a 3.6 Å π-π stacking distance between the triphenylene units [236-243]. A comparison of the 2 dendrimers' computed radii indicates that the arrangement of the dendrons around the cores, as permitted by their individual hydrocarbon spacers, is what gives them their distinct characteristics. The dendrons in the compound with the shorter spacer provides a steric shield around the core, which stops neighboring molecules from stacking π-π to form columns [244-250]. The bulky end groups can fit in the area surrounding the cores of the bigger molecule because the spacers are looser. As organic templates in biomimetic mineralization processes, chiral amphiphilic liquid crystalline dendrimers like these are expected to find use. The term "glycodendrimer" refers to dendrimers that have carbohydrates in their structure [251-255]. A Glycodendrimers dendrimer is seen in **Figure 9**.

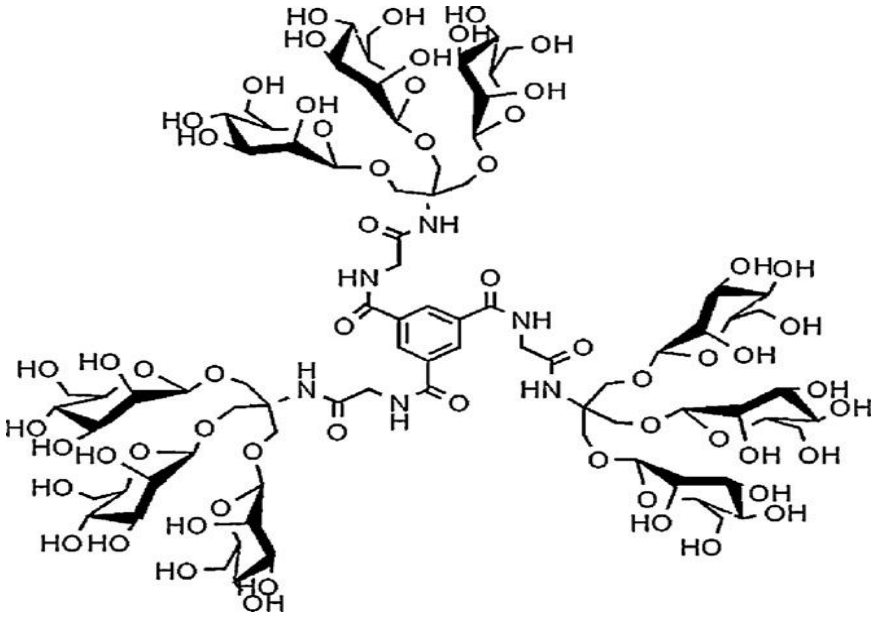


Figure 9 Carbohydrate-coated glycodendrimer [1].

PAMAM Dendrimers

PAMAMs, which are widely used in medication delivery, are one kind of dendrimer. A dendrimer PAMAM with 3 generations [101-103] is shown in **Figure 5**. Many PAMAM dendrimers with changed levels have changeable end amines that may bind to various guest or target molecules, are water soluble, and do not stimulate the immune system [104-106]. Because of its special structure, which includes triple amine and amide linkages, PAMAM dendrimers' interior cavity may accommodate metal or guest molecules [256-260]. The PAMAM Dendrimers are shown in **Figure 10**.

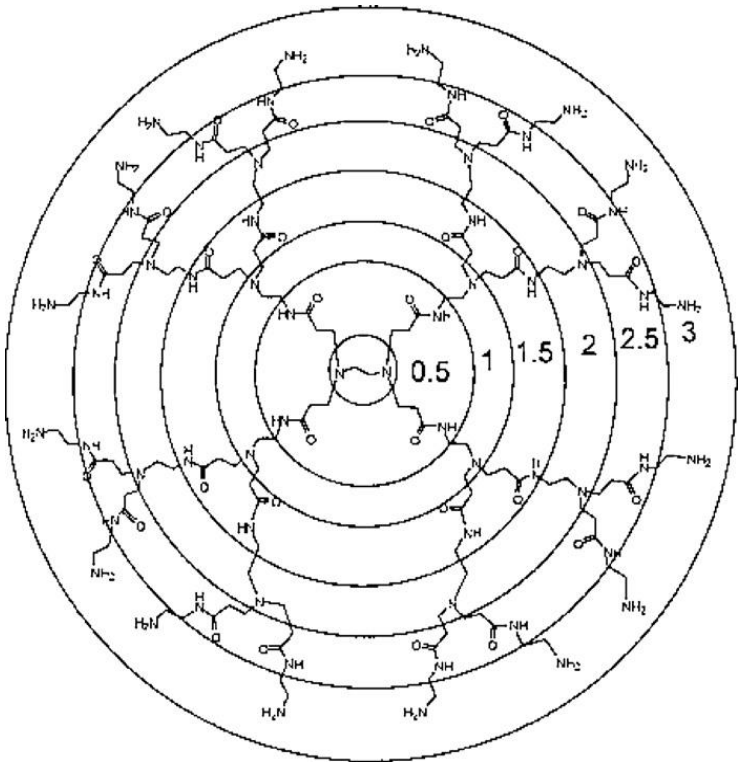


Figure 10 3 Generation (G3) PAMAM Dendrimer [38].

Mechanisms of drug loading in dendrimer carriers

Physical encapsulation of drug molecules

The ability of dendrimers to encapsulate guest molecules in their interior cavities is one of its most significant characteristics. Vogtle *et al.* nvestigations (**Figure 11**) [1-4,111-114] showed the first physical encapsulation of low-soluble drug molecules in the empty cavity of dendrimers. The hydrophobic drug attaches to the non-polar nucleus through hydrophobic interactions when the polymer and drug solution are simply combined [42,115-117]. A series of non-covalent interactions, including hydrophobic forces, hydrogen bonds, spatial barriers, and electrostatic interactions, regulate the release of encapsulated molecules in the aqueous medium once physical contact between the host and dendrimeric carrier molecules has been established [43,118-121]. The polymer's structure, particularly the inner cavity's characteristics, must be carefully taken into account in order to optimize the loading capacity of medicinal molecules by dendrimers [44,261-264].

Figure 11 Drug compounds that is hydrophobic within holes [43].

Chemical binding of drug molecules

In order to regulate and briefly release bound medications, anticancer drugs chemically connect to dendrimer surface groups [126,127]. Numerous anticancer medications and imaging substances can attach to dendrimers due to their numerous surface groups and adaptable chemical structure [265-270]. However, the dendrimer's spherical and compact shape is preserved in solution (**Figure 12**).

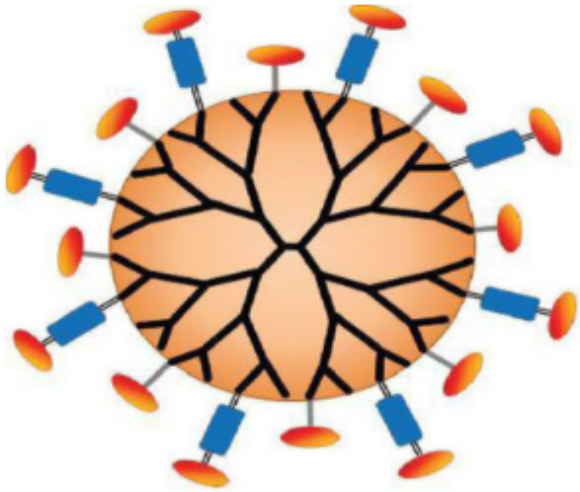


Figure 12 Drug molecules on the surface of dendrimers (red) [45].

Direct connection of the drug to the dendrimer

This technique uses receptors on the dendrimer surface to capture drug molecules by a variety of junctions [271-274]. According to experiments, the dendrimer binding process primarily enhances the solubility of the loaded medication in the case of some therapeutic compounds, such as anticancer treatments, but restricts the drug's release and anticancer efficacy in both clinical and laboratory settings. One essential factor in preventing their start is the presence of an anti-cancer medication on the dendrimer's surface [48,12-134].

Light sensitive connection

The antennae on dendrimers are made to receive light. Absorption pigments on the outer surface of these dendrimers transport light energy to other pigments in the nucleus [275-279]. The cavity may open or close in response to light from the dendrimer optical receptors, allowing the trapped drug to either be released or absorbed [280-282]. Archut *et al.* published an example of such optical antennas. Photochemical pore opening occurred in the dendrimer (polypropylene imine with the 32-end group of azobenzene) (**Figure 13**). This dendrimer's azobenzene groups can be reversed by optical isomerization. When exposed to 313 nm light, isomer E transforms into Z form; at 254 nm or heat, it reverts to its original isomeroulia, E. These dendrimers can serve as a light-switching host for eosinY, a red crystalline powder with the formula C20H8O5Br4 that is employed in biology to stain cells when combined with sodium or potassium ions. Guest molecules are released as a result of these photochemical alterations on the dendrimers' surface [283-287].

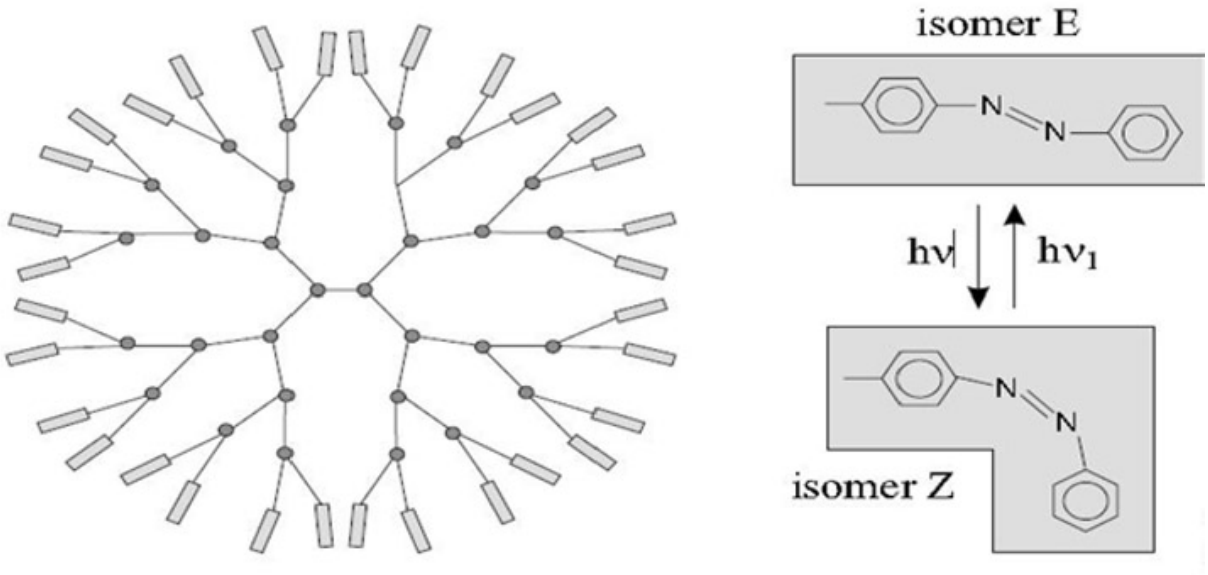


Figure 13 A sample of azobenzene E, Z isomers and a dendrimer with terminal azobenzene groups [1].

Dendrimer drugs

Dendrimers may readily pass through biological barriers because of their nanoscale size. By bonding, this characteristic enables dendrimers to retain host molecules within or on their surface [54].

Dendrimers in dermal drug delivery

Dendrimers have recently been used in dermal delivery methods. Hydrophobic groups in the structure of bioactive medications typically decrease their water solubility and hinder efficient drug delivery to cells. Conversely, dendrimers, which are extremely biocompatible and water-soluble, might enhance the solubility and efficient delivery of medications [288-292]. Although nonsteroidal anti-inflammatory medicines (NSAIDs) are particularly successful in treating osteoarthritis and both acute and chronic rheumatism, their clinical usage is frequently restricted by intestinal, gastrointestinal, and renal adverse effects when administered orally. These negative effects are avoided by dermal treatment, which also keeps the blood's healing level stable for a long period. The poor distribution rate caused by skin barriers is one of the drawbacks of dermal delivery. In lab experiments on rat skin that had been injured, ketoprofen attached to PAMAMG5 dendrimers revealed that the secretion of ketoprofen from the ketoprofen-dendrimer complex was 1.5 times more than that of ketoprofen contained in regular saline. Rats were used to test the medications' analgesic effects. According to the findings, pure ketoprofen lowers pain feelings between 2 and 5 h after dermal administration, but the ketoprofen-dendrimer complex reduces pain within 2 to 3 h [55,56,145-147]. A number of variables, such as generation size, dendrimer concentration, pH, core, and internal branching, influence the solubilization of NSAIDs [87]. A number of NSAIDs have been effectively complexed with or encapsulated into various dendrimers; **Table 2** displays the findings of these investigations. **Table 3** displays the findings of scientific research on the use of both modified and unmodified dendrimers in the administration of anticancer medications.

Table 2 Dendrimers as carriers of NSAIDs.

Drug	Type of dendrimer	Effects of conjugation
Indometacin	4-Carbomethoxy-pyrrolidone PAMAM	[201,202]
Ibuprofen	Resorcinarene- PAMAM dendrimers	[203]
Ketoprofen	Peptide dendrimers	[204]

Drug	Type of dendrimer	Effects of conjugation
Celecoxib (COX-2 inhibitor)	Biotinylated PAMAM G3 dendrimers	[205,206]
Ketoprofen	PAMAM dendrimers	[207]
Diclofenac	Polyamidoamine dendrimer	[208]
Ibuprofen	Cationic carbosilane dendrimers	[209]
Piroxicam	PPI dendrimers	[210]
Ketoprofen	PAMAM dendrimers	[211]
Flurbiprofen	Poly(epsilon-lysine) dendrimers	[212]

Table 3 Dendrimers as carriers of anticancer drugs.

Drug	Type of dendrimer	Effects of conjugation
Docetaxel	Trastuzumab-grafted PAMAM dendrimers	[213]
Docetaxel or Paclitaxel	PAMAM-trastuzumab dendrimers	[214]
Cisplatin	PAMAM dendrimers	[215]
Paclitaxel	PEGylated PAMAM dendrimers	[216]
Paclitaxel	Octa-arginine modifed PAMAM dendrimers	[217]
5-Fluorouracil	PAMAM dendrimers	[218]
Methotrexate	Glycosylated one-step PAMAM dendrimers	[219]
Doxorubicin	β-cyclodextrin-decorated PAMAM dendrimers	[220]

Oral delivery of dendrimers

Due to its significant advantages and positive patient feedback, the oral medication administration system has long been regarded as the most popular approach [148]. However, this system's shortcomings include limited intestinal barrier penetration and low water solubility [292-296]. It was investigated how well the insoluble medication naproxen penetrated the epithelium [148,149]. The stability of the medication attached to the G0 PAMAM dendrimer was examined in 80 % of human plasma and 50 % of homogenized liver. According to the findings, the inactive medication was held via the lactate ester linkages in the homogenized liver with delayed hydrolysis and great plasma stability [150]. The pair could be eligible for a restricted release. The resultant pair will have great chemical stability if diethylene glycol binders are utilized, but it will release the medication into the liver and homogenized plasma very soon. As a result, these pairings improve oral absorption as nano carriers [1-4,56-58].

Dendrimers in ocular drug delivery

Everyone agrees that intraocular medications have a limited bioavailability. The evacuation of the solution by tears and the drainage of extra fluid via the nasal mucosa are the causes of this problem. Sterile, isotonic, biocompatible, and bioavailable systems are ideal for ocular medication administration and should not be disregarded. Complex issues with medication distribution in the eyes can be effectively resolved by dendrimers. PAMAM dendrimers with carboxyl or hydroxyl surface groups have been used in recent studies to extend the shelf life of pilocarpine in the eye [59,151-153].

Dendrimers in pulmonary drug delivery

Pulmonary medicine has also made use of dendrimers. The effectiveness of PAMAM dendrimers in boosting enoxaparin's pulmonary absorption was examined in one research. The absorption of enoxaparin is increased by 40 % by positively charged PAMAM dendrimers of generations G2 and G3. This effect is

absent in G2.5 PAMAM, a half-generation dendrimer with negatively charged carboxyl groups [59,154-156].

Dendrimers in targeted drug delivery

Due to the non-selective use of extremely powerful medications, general cancer chemotherapy is currently less successful in treating tumors. An alternate method of treating cancer that also increases therapeutic indicators and decreases medication resistance is to target tumor cells with drug delivery devices [59,157-160].

Because of their perfect characteristics, dendrimers can be used in targeted drug delivery systems. Folic acid is among the most potent targeted agents that dendrimers can provide. Many different kinds of cancer cells have membrane folate receptors, which are proteins attached to folate that are widely distributed on their surfaces. PAMAM dendrimers bind to fluorescein isothiocyanate for imaging and folic acid to target tumor cells. The complementary oligonucleotide is then where the 2 molecules bind. Different medications can be coupled with various targeting and imaging agents because to this DNA-dendrimer aggregation. In a different trial, methotrexate was linked to dendrimer-bound folic acid, which was utilized as the targeted agent. The kit was administered and tested on animals with human KB tumors and compromised immune systems. The proportion of administered dosage, particularly in tumor cells, is demonstrated by bio-dispersion tests employing a targeted polymer complex (including folic acid, tetrahydrofolic acid, folic acid-(glutamic acid-13C5), vitamin B12, and biotin). Additionally, on the first day following injection, the dendrimeric complex is quickly and clearly removed through the kidney [59,161-163].

Dendrimers for controlled drug release

Units of polyethylene glycol (PEG) affixed to the dendrimer surface were utilized to enhance the solubility in water. G3 PAMAM dendrimer was attached to PEG. The produced kit contained methotrexate, which was then evaluated for drug release in a dialysis bag [164,165]. In contrast to the unencapsulated medication, the PEG-dendrimer complex conjugates with the encapsulated drug and extends the release of methotrexate. Four G4 (PAMAM) dendrimers with an amino end allow for the controlled release of fluoroprofen [166,167]. The constructed dendrimeric set demonstrates that the drug loaded has a gradual release after a quick initial release [1-4,52-59].

Dendrimers for diagnostic applications

Dendrimers come in more than 50 families, each with special characteristics and a range of applications for their outer, inner, and core surfaces. Diagnostic techniques also make use of dendrimers [168-170]. A novel approach to cardiac testing has been established by Dade International. Using this technique, dendrimers affix the blood sample's proteins to immunoglobulins that are adhered to glass. The findings will be displayed if the heart muscle is damaged. The wait time for blood test results is greatly shortened to around 2 min using this technology [171-173]. When conducted in a dendrimer-free IgG solution, the same test takes longer than 2 min. Additionally, the test's sensitivity and accuracy are increased when dendrimers and antibodies are paired. Dendrimers can be utilized as a timed-release device for biologically active substances or as a coating agent to protect or distribute medications to particular parts of the body [174-177].

Although fluorouracil (5FU) is extremely toxic, it has good anticancer efficacy. PAMAM acetylated dendrimers lessen the toxicity of 5FU by slowing its release. Anticancer medications seem to be well transported by these dendrimers. Preclinical research has examined dendrimers as a differentiator for nuclear magnetic resonance imaging (MRI). The method's sensitivity and specificity are increased by the inclusion of a differentiating agent, such as paramagnetic metal cations [1-4].

Biomedical applications

Cancer therapy

Today, the types of treatments for treating cancer patients have saved many. However, the side effects of treatment are stiff and affect the whole body due to the nonspecificity of the chemotherapeutic agent. Cancer is a very complex biological phenomenon and can be considered a disease of many diseases. One indicator of low-club cells is that they become rapidly and out of control and do not proliferate. Current chemotherapy primarily aims to destroy all cells that are split rapidly.

The drawback of this treatment is that other body cells, such as the hair follicles and intestinal epithelium, also grow rapidly. Therefore, patients will be able to deal with life-changing side effects. The development of nanoparticles offered new possibilities for chemotherapy. Intelligently designed nanoparticles target targeted drug collection in tumors or specific groups of cells to avoid toxic effects of other normal tissues and organs. Several systems have been tested to provide this type of treatment [216].

Micelles and liposomes provide another option for the submission of chemotherapeutic agents. Furthermore, micelles are also the best way to dissolve insoluble drug therapy due to their hydrophobic core and hydrophilic shell. As the surface of micelles continues to be pegylated, the Nano craters increase the ability to pass passive transport, resulting in higher drug concentrations of the tumor. From now on, there are several polymers, including anticancer drugs, NK012, NK105, NK911, NC-6004, SP1049C, under clinical research and such systems, under the genexol PM (Paclitaxel) [217].

Dendrimers are highly branched polymers, and their absorption, distribution, metabolism and removal (ADME) with many functional groups available for adhesion of drugs, targeting agents and imaging agents depends on a variety of structural features. It was reported in polyfunctional dendrimer systems for localization (folic acid), imaging (fluorescein), and treatments of anticancer drug methods. Dendrimer-based nanoplatelet therapeutics can use biocompatible components to improve the therapeutic index of cytotoxicity, and improve surface modification using pegylation, acetylation, glycosylation, and various amino acids [218].

Diagnostic testing

The use of nanoparticles for diagnostic purposes is an area that is currently unavailable for clinical applications, but is highly explored in science. Current techniques for diagnostic testing due to insufficient fluorescent markers provide answers for fluorescent nanoparticles to overcome these complaints, including individual use, color adjustment, color adjustment due to bleeding effects, and limited use of dyes [219].

Recently, thermal nanoparticles, nanoparticles, which can be used for treatment and diagnosis, have been paying a lot of attention. This strategy was realized with many classes of nanoparticles, including drug conjugation, dendrimers, tension aggregation (micelles and vesicles), core-shell particles, and carbon nanolars. By suppressing drugs and images with different smart formulations, the pathways and localization of these nanoparticles can be monitored to target and drug reality to assess treatment response [220].

Nutraceutical delivery

Nutraceuticals is a food and is a standardized component with outstanding health benefits. They are usually consumed as supplements to various allopathic treatments, achieving additional health benefits and reducing the risk of several chronic diseases. Like other drugs, the effectiveness of orally consumed nutrients is affected by interactions between food matrix, water solubility, degradation/metabolism, and epithelial permeability. Most nutrient fluids are lipophilic molecules such as fat-soluble vitamins (A, D, E and K), multiple lipids and other phytochemicals. Nanotechnology once again provides extensive support, with most studies aimed at improving the resolution mechanism of nutrients through nanoparticles [221].

Anti-inflammatory, antioxidant, anti-apoptotic, and anti-angiogenic, among which the best known and examined nutrients, anti-apoptotic and numerous nutritional supplements for testing are curcumin (daibirroylmethane). Because it is essentially water-insoluble and has very poor bioavailability, various methods have been implemented to tackle this problem, such as liposomes, phospholipid vesicles, and polymer-based Nano oxidation. 9 times oral bioavailability of curcumin was observed compared to curcumin played with pipeline (absorption amplifier). Another study of colloidal nanoparticles from curcumin synchronized relative to curcumin powder showed a 40-fold higher region under the curve (AUC), indicating healthy, healthy human and inhibitory effects on alcoholism [222].

Photodynamic therapy

Photodynamic therapy (PDT) is based on the activation of photo scleritis with visible or near-infrared

(NIR) light. During the proposal, a very energetic state is formed. This provides highly reactive singer saliva that can induce necrosis and apoptosis of tumor cells after reaction with oxygen. Dendritic delivery of PDT active ingredients has been investigated in recent years to improve tumor selectivity, retention and pharmacokinetics [72-75].

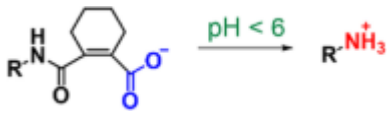
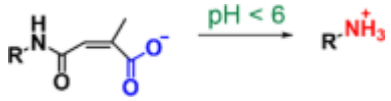
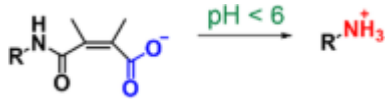
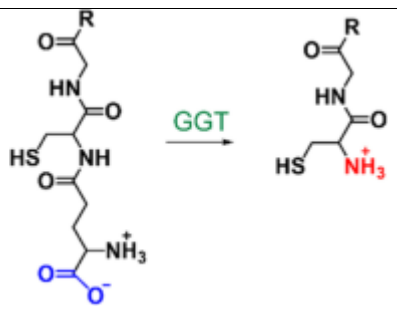
Dendrimers used for enhancing solubility

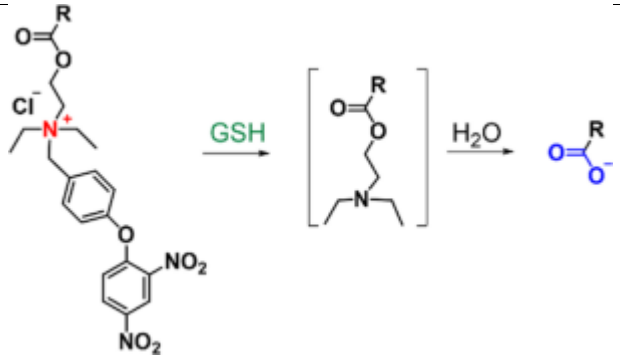
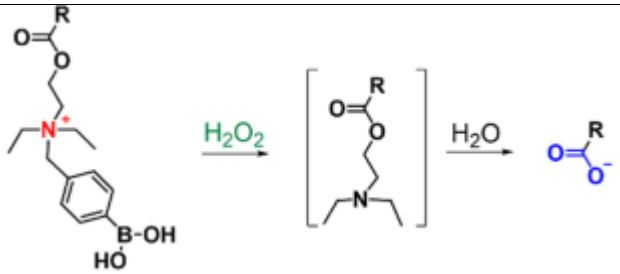
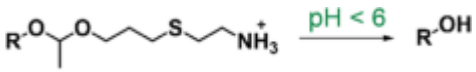
PAMAM Dendrimer is expected to have potential uses to improve the solubility of pharmaceutical delivery systems. Dendriere has hydrophilic exteriors and interiors that cause the properties of its monomolecular micelles. The dendrimer-based airline offers opportunities to improve oral bioavailability of problematic drugs. Thus, Dendrimer-Nano supports the potential to improve the solubility of efflux transporters and/or bioavailability of medicinal products that are substrates [70,71].

Surface stealth modification during body circulation: Charge-reversal dendrimers

Another idea is to deactivate the cationic surface charges of dendrimers during blood circulation to minimize the nonspecific cellular uptake and adsorption and then reactivate the positive surface charges once inside the target tissues or cells. This is the basis for making charge-reversal or charge-switchable dendrimers. Cues including temperature, pH, osmotic pressure, and biological signals may be utilized to reverse charges on the dendrimer surface [85-91]. We summarize the recently reported charge-reversal chemistries in **Table 4**. In general, the transformation from negative charge to positive charge is conducive to the stability of the materials in the blood circulation and their endocytosis, while the transformation from positive charge to negative/neutral charge is helpful to improve the release of nucleic acids.

Table 4 Surface charge-reversal chemistries.

Charge reversal	Chemistry	Stimuli	Ref
Negtive ⬇ Positive		pH	[297]
Negtive ⬇ Positive		pH	[297]
Negtive ⬇ Positive		pH	[297]
Negtive ⬇ Positive		Enzyme: γ-glutamyl transpeptidase (GGT)	[298-300]

Charge reversal	Chemistry	Stimuli	Ref
Positive ⬇ Negtive		ROS	[301]
Positive ⬇ Negtive		ROS	[302]
Positive ⬇ Neutral		pH	[303]

Applications in different routes of drug administration

Now, dendrimer-drug complexes or conjugates have already been evaluated in different routes of drug administration systems, such as intravenous/intraperitoneal/intratumorally, oral, transdermal, and ocular drug delivery systems (**Tables 5** and **6**). Before conducting applications of dendrimers in clinical or preclinical trails, we should consider "Which is the most suitable administration route for the prepared dendrimer-drug formulation ?" and discuss the safety or benefits of administration of the formulations in these routes. Biodistribution and pharmacokinetics are key factors in clinical trials of these applications. In this issue, these problems will be well expatiated by detailed applications.

Table 5 Proposed applications of dendrimers in intravenous/intraperitoneal/intratumoral drug delivery routes

Guest molecules	Dendrimers	Interaction pattern	Goal	Administration route	Ref
Cisplatin	G3.5 PAMAM	Conjugation	Cancer chemotherapy	Intravenous	[56]
5-Fluorouracil	PEG modified G4 PAMAM	Simple encapsulation	Pharmacokinetic studies	//	[80]
Indomethacin	G4 PAMAM	Electrostatic interaction	Anti-inflammatory	//	[81]
Flurbiprofen	G4 PAMAM	//	Anti-inflammatory	//	[82]
Primaquine phosphate	Galactose coated PPI	Simple encapsulation	Liver targeting	//	[83]

Guest molecules	Dendrimers	Interaction pattern	Goal	Administration route	Ref
Methotrexate	Folic acid coated PAMAM	Conjugation	Cancer chemotherapy	//	[76]
Boron	EGF conjugated PAMAM	//	Boron neutron capture therapy (BNCT)	//	[89]
//	//	//	BNCT	Intravenous and intratumoral	[88]
//	//	//	BNCT	Intratumoral and convection enhanced delivery	[70]
//	Antibody conjugated PAMAM	//	BNCT	Intraperitoneal	[86]
//	Antibody conjugated PAMAM	//	BNCT	Intratumoral	[68,69]
Glucosamine	G1 PAMAM	//	Biological modulators	Intraperitoneal	[66]
Porphyrin	5-Aminolaevulinic acid	//	Photodynamic therapy	Intraperitoneal	[64]
DNA	G9 PAMAM	Electrostatic interaction	Lung gene transfection	Intravenous	[90,91]
//	PAMAM-cyclodex-trin conjugate	//	Spleen gene transfection	//	[90]
//	Mannose-PAMAM-cyclodextrin conjugate	//	Kidney gene transfection	//	[92]
111In-labeled oligo-DNA	G4 PAMAM and G4-biotin conjugate	//	Kidney and lung gene transfection	//	[93]
DNA	PAMAM dendrimers and avidin	//	Tumor targeting	Intraperitoneal	[67,71]
DNA	PPI	//	Liver gene transfection	Intravenous	[94]
DNA	PPI with methyl quaternary ammonium	//	Liver gene transfection	//	[95]
Gene medicine	G3 PPI	//	Intratumoral gene transfection	//	[94]
DNA	PEG modified PPI	//	Transfection agents for DNA enzymes	//	[96]
DNA	PAMAM	//	Inhibition of tumor growth and angiogenesis	Intratumoral	[95]

Table 6 Proposed applications of dendrimers in oral/transdermal/ocular drug delivery routes.

Guest molecules	Dendrimers	Interaction pattern	Goal	Administration route	Ref
—	Lipidic dendrimer	—	Absorption ability by different tissues	Oral	[100]
—	Various PAMAM dendrimers	—	Intestine uptake of PAMAM dendrimers	Oral	[101]
—	Polylysine dendrimer	—	Oral uptake and translocation	Oral	[102]
Propranolol	G3 PAMAM	Conjugation	Improve oral bioavailability	Oral	[104]
5-Fluorouracil	Fatty acid and phospholipid coated PAMAM	Simple encapsulation	Improve oral bioavailability	Oral	[105]
Ketoprofen	G5 PAMAM	Electrostatic interaction	Anti-inflammatory and improve oral bioavailability	Oral	[106]
Tamsulosin hydrochloride	G3 PAMAM	Simple encapsulation	Enhance transdermal delivery efficacy	Transdermal	[110]
Tamsulosin hydrochloride	G2.5 and G3 PAMAM	Simple encapsulation	Transdermal mechanism	Transdermal	[111]
Indonmethacin	G4 and G4.5 PAMAM	Electrostatic interaction	Anti-inflammatory	Transdermal	[52]
Ketoprofen and diflunisal	G5 PAMAM	Electrostatic interaction	Anti-inflammatory	Transdermal	[112]
CAT reporter transgene	PAMAM	Electrostatic interaction	Skin gene transfection	Transdermal	[113]
Pilocarpine nitrate and tropicamide	PAMAM dendrimers	Simple encapsulation	Miotic activity and mydriatic activity	Ocular	[115]
Glucosamine and glucosamine 6-sulfate	G3.5 PAMAM	Conjugation	Prevent scar tissue formation	Ocular	[122]
Collagen	G2 PPI	Conjugation	Corneal tissue-engineering scaffold	Ocular	[123]
Collagen	Cell adhesion peptide modified PPI	Conjugation	Corneal tissue-engineering scaffold	Ocular	[124]
ODN-1	Lipid–lysine dendrimers	Electrostatic interaction	Prevent ocular neovascularisation.	Ocular	[126]

Conclusions and future research

A high degree of branching, a well-defined molecular weight, a globular shape, and nanoscale size are some of the characteristics that identify dendrimers. Based on their structural characteristics, dendrimers may be classified into distinct categories that offer innovative delivery systems for a range of medicinal substances. Dendrimers are an excellent choice for nanomedicine, especially drug delivery, due to their appealing qualities, which include strong control over branching length, size, and form as well as tremendous design flexibility. Drugs can be successfully integrated into dendrimers' structure through a variety of interactions due to the promising structure of dendrimers. Dendrimers can be used to increase a drug's permeability, toxicity, solubility, bioavailability, and biocompatibility. Researchers have focused a lot of emphasis on the benefits that dendrimer nanostructures offer, not only in drug delivery but also in illness detection and treatment. Dendrimer-based nanomedicines have seen a significant increase in patents and scholarly publications recently. Many of these nanomedicines are either in clinical studies or have been marketed. Certain items are anticipated to go through clinical trials in the future due to the quick advancements in dendrimer-based nanomedicines. The analytical characterization and scale-up creation of dendrimers and their products are 2 difficulties that arise in the use of dendrimer-based nanomedicines. Advanced analytical techniques may be required to fully define the produced product due to the complicated structure of dendrimers and their complexes or conjugates with ligands or medicines. Furthermore, because dendrimer synthesis often requires many procedures, the scale-up generating process presents another significant barrier in the development of dendrimer-based nanomedicines. For manufacturing to scale up, dendrimer production must be highly stable and reproducible. Hopefully, this overview of dendrimer uses in nanomedicine clarifies the potential of dendrimers and confirms a higher degree of hope for their future use in drug delivery, diagnostics, and treatment.

Interest in dendrimer chemistry has grown ever since the first dendrimer was created. The creation of well-controlled dendrimer structures with a large number of surface groups is the result of advancements in synthetic and controlled polymerization processes. This article discusses dendrimers in a very specific manner and outlines 2 methods for preparing them: Divergent and convergent. We shall familiarize ourselves with the characteristics and varieties of dendrimers in this text.

Generally speaking, dendrimers can contain biomolecules or medications within their cavities or on their surface. One of dendrimers' properties is the regulated release of their host molecules into the target tissue, which can help reduce medication consumption and some of its negative consequences. They do, but they also possess qualities that make them highly appealing. Dendrimers are perfect carriers for various applications because of their controllable characteristics, which include size, shape, branch length, and surface qualities. Depending on the kind of medicine, drug delivery may occur through the skin, mouth, eyes, or lungs. The dendrimer can also be helpful in the diagnostic process and can contain imaging agents and anticancer medications. The processes of drug loading in dendrimer carriers vary.

Nanomedicine is currently one of the most exciting areas of research. Using a variety of nanoparticles to deliver precise amounts of drugs to damaged cells, such as cancer cells, without disrupting the physiology of normal cells, the use of nanomedicine and nanodrug delivery systems is certainly a growing trend. The examples of nanoparticles shown in these communications are not uniform in size, some of which are truly measured in nanometers while others are measured in the sub-micrometer range (greater than 100 nanometers). The use of metallic nanoparticles, including gold and silver, in both diagnostics and therapy is an area of research that could potentially lead to a wider application of nanomedicines in the future. One of the main interests in this direction involves gold nanoparticles, which appear to be well absorbed into soft tumor tissues and render the tumor susceptible to radiation (e.g., in the near infrared region). Despite the widespread understanding of the future prospects of nanomedicine and nanodrug delivery systems, their actual impact in the healthcare system, even in cancer treatment/diagnosis, remains very limited. This is because this field is a new field of science with only 2

decades of real research on the subject and many key fundamental properties are still unknown. Basic markers of diseased tissues, including key biomarkers that allow absolute targeting without altering the natural cellular process, are a major area of future research. Ultimately, the application of nanomedicine will advance with our increasing knowledge of diseases at the molecular level or the identification of markers comparable to the size of subcellular nanomaterials to open avenues for new diagnostics/therapy. Hence, understanding the molecular signatures of disease will lead to future advances in nanomedicine applications. The concept of controlled release of specific drugs at confined sites, the technology to assess these events, the effect of the drug at the tissue/cellular level, as well as the mathematical theoretical models of prediction are still to be perfected. Several studies in the field of nanomedicine have focused on biomaterials and formulation studies, which appear to be the early stages of biomedical applications. Valuable data in potential applications as therapeutic and diagnostic drug studies are obtained from animal studies and multidisciplinary research, which requires significant research time and resources. With the growing global trend towards more precise drug discovery and diagnosis, the future looks bright for a smarter and more multidisciplinary approach to nanomedicine and nanodrug delivery. There is great enthusiasm with the view of simplifying the development of nanorobots (and nanodevices) that function in tissue recognition and repair mechanisms with complete external control mechanisms. However, like their benefits, the potential risk of nanomedicines to both humans and the environment in general requires long-term study. Hence, appropriate impact analysis of the possible acute or chronic toxic effects of new nanomaterials on humans and the environment should be analyzed. As nanomedicines gain popularity, their cost-effectiveness is another area of investigation that requires further research input. Initially, the use of nanotechnology was mainly based on increasing the solubility, absorption, bioavailability and controlled release of drugs. Good examples of therapeutic application of nanotechnology are berberine, curcumin, ellagic acid, resveratrol, curcumin and quercetin. The efficacy of these natural products has been greatly improved through the use of nanocarriers formulated with polymeric nanoparticles of gold, silver, cadmium sulfide and titanium dioxide along with solid lipid nanoparticles, crystal nanoparticles, liposomes, micelles, superparamagnetic iron oxides and iron nanoparticles. There has been a continuous demand for new natural biomaterials due to their biodegradable, biocompatible, readily available, renewable and low toxicity qualities. One of the great interests in the development of nanomedicine in recent years is related to the integration of therapy and diagnostics (theragnostic), an example of which is cancer as a disease model. Good examples include iron oxide nanoparticles encapsulated with oleic acid for near-infrared diagnostic applications. Since the 1990s, the list of nanotechnology-based products and FDA-approved clinical trials has grown exponentially, including synthetic polymeric particles. Liposome formulations; micellar nanoparticles; protein nanoparticles; nanocrystals, and many others are often combined with drugs or biologics. Although regulatory mechanisms for nanodrugs, along with safety/toxicity assessment, will be the subject of further development in the future, nanomedicine is already revolutionizing the way drugs are discovered and administered in biological systems.

Dendrimer-based drug delivery systems are poised for significant advancements, particularly in the context of emerging therapeutic modalities such as biologics and RNA-based therapies. The unique structural properties of dendrimers allow for precise drug targeting and controlled release, making them suitable carriers for a variety of therapeutic agents. Dendrimers can be tailored for specific drug delivery needs through surface modifications, enhancing biocompatibility and targeting capabilities. Recent studies have demonstrated their effectiveness in delivering small molecules, peptides, proteins, and genetic materials, particularly in overcoming barriers like the blood-brain barrier. Dendrimers are increasingly utilized in cancer therapy, serving as carriers for chemotherapeutics, siRNAs, and nanoparticles, with modifications that improve targeting and reduce side effects. Their versatility allows for combination therapies, integrating multiple treatment modalities such as chemotherapy and gene therapy. The potential of dendrimers in delivering biologics and RNA-based therapies is significant, as they can encapsulate and protect these sensitive molecules,

enhancing their stability and bioavailability. Innovations in dendrimer formulations are expected to facilitate the development of novel therapeutic strategies, particularly in personalized medicine. While dendrimers show promise in enhancing drug delivery, challenges remain in scalability and regulatory approval, which may hinder their widespread application in clinical settings. Continued research is essential to address these barriers and fully realize the potential of dendrimer-based systems in modern therapeutics.

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