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Review

Dendrimers as drug delivery vehicles: a comprehensive review

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Abstract

Dendrimers are chemical compounds that have functional groups on their surface and a hyperbranched structure. It is simple to promote the functionality of dendrimers and produce a variety of biocompatible products by altering their terminal groups. These materials have exceptional physicochemical characteristics that make them more beneficial in the administration of medications. They have a vigorous amount of potential as agents for nanomedicine applications because of their rare properties, which compose internal cavities, strong reactivity, globular form, solubility in water, and nanoscale size. They might also be synthesized easily. In-depth information about dendrimer composition and classifications, synthesis, and applications in nanomedicine, particularly drug delivery, is mentioned in this paper. Dendrimers are chiefly categorized by their functional groups, which permit for concise encapsulation of active compounds and structural imitatively of biomaterials. A rare property not often seen in other polymers serves to stabilize the surface of dendrimers to broaden their solubility in water. Dendritic molecules own a different variety of applications, such as dendrimers, dendrons, dendronized polymers, and hyperbranched polymers, which are organized based on their molecular weight. The role-play of dendrimers' is the capability to attach a broad range of chemical entities and their ability to shift pharmacokinetic and pharmacodynamic features through tailored drug delivery. To sum up, this study bolded how dendrimers' intricate structure and versatility make them excellent drug delivery vehicles since they may exactly modify their properties to reach special requirements. Drugs can be aimed at neuroinflammatory disorders and made more soluble and stable by dendrimers, which also deliver for a diversity of modes of delivery. Additionally, they show attractive ability in gene transfection and sensor production, drawing near their potential for a difference of usages in industries including pesticide delivery and medicine. With the potential to send out gene therapy, medicine delivery, and other specialties of science and medicine, dendrimers are becoming a huge crucial in the pharmaceutical and medical industries through the next research and clinical investigations.

Keywords: Dendrimers, Dendrons, PAMAM, Drug delivery, Nanomedicine, PPI dendrimers.

1. Introduction

Dendrimers are organic nanostructures that have unique physicochemical properties and are biocompatible, making them valuable for drug delivery [1]. Their unique framework for drug administration is derived from their ability to be precisely modified in terms of size, shape, and branching length. [2]. Also have a hyperbranched, globular shape. Nanomedicine is a new discipline that uses man-made materials measuring 100 nm or smaller to enhance and preserve human health. Nanomedicine encompasses a wide range of nanomaterials and nano-structures, including nano-particles, nanotubes, nanoporous membranes, nanofibers, and more [3].

The term dendrimer is derived from the Greek word dendron, which means "tree," because its morphological structure resembles that of tree branches. It also incorporates the Greek word meros, meaning "part" [4]. The initial dendrimer-like chemical, poly (propylene imine) (PPI), was originally documented by Fritz Vogtle et al. in 1978 using diverging technology, and later by Donald Tomalia et al. in the early 1980s [4]. Dendrimers consist of multiple layers of dendrons, which are branching units, extending from a central starting core. Each layer represents a generation [5, 6]. The exact and regulated process of repeated synthesis, along with the number of functional groups present in both the intermediate and peripheral layers, are primarily responsible for dendrimers' extraordinary structural stability. [7]. Dendritic polymers, such as PPI dendrimers and Polyamidoamine (PAMAM), have been used as drug carriers; their usefulness includes aimed administration and activated solubility. All things believed dendrimers have demonstrated potential for a variety of therapeutic applications as drug delivery methods [4]. Cationic charges in dendrimers could indeed pose a toxicological hazard, mainly due to their connections with cell membranes, inducing cellular disruption and cytotoxicity.

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In biological systems, this toxicity is clearly apparent in cationic dendrimers, which may have hemolytic and other opposing effects. As an alternative, strategies including surface modification and the development of biodegradable dendrimers can lessen these negative consequences. In terms of toxicity mechanisms for instance, through cell membrane interaction, cationic dendrimers cause hemolysis and cytotoxicity by rupturing cell membranes[8]. Moreover generation and charge dependency compared to their anionic or neutral counterparts, higher-generation dendrimers with positive surface charges show increased cytotoxicity[9]. To address this, strategies for mitigation by adding neutral or anionic groups to dendrimer surfaces, surface engineering can reduce toxicity without compromising the effectiveness of treatment. Additionally dendrimers' negative impacts can be reduced by using biodegradable materials[8]. Therefore, because cationic dendrimers may cross cell membranes, they may be used to transport drugs; however, because of their inherent toxicity, their use in biomedical applications needs to be carefully considered and adjusted.

Because of their potential for regulated drug administration and personalized therapy, dendrimers have been the subject of much research in recent years [10]. They have been made to treat ocular illnesses, penetrate the cornea to distribute medications, and get beyond the barrier of the cornea's impenetrability [11]. Moreover, fluorescence-tagged FITC-PAMAM dendrimers have been made; these dendrimers need to provoke antiproliferative activity and facilitate intracellular medication administration [12, 13]. Due to their near-monodispersity, easy multifunctionalization, and clearly defined chemical structure, dendrimers show a piece of evidence for therapeutic drug delivery [14]. Their structure is spherical and hyperbranched. PAMAM and PPI dendrimers are instances of dendritic polymers that have been applied as drug carriers; they have advantages including enhanced solubility and precise delivery. In contrast, dendrimers' cationic charge may pose toxicity issues. All objects considered, dendrimers have shown a clear state as drug delivery systems with a range of therapeutic uses [4].

Dendrimers have worked strongly with the potential to enhance the biological and physicochemical qualities of pharmaceuticals, such as promoted solubility, bioavailability, and drug aiming, by sending out medications to their intended locations at lower dosages [15, 16]. They also have the potential to minimize drug-related toxicity and increase drug safety [17]. The intricate physiology of the eye illustrates a unique challenge for the improvement of innovative ocular medication delivery systems: passing by the several barrier mechanisms stacked throughout the organ [18, 19]. Therapeutic delivery systems (DDSs) based on nanotechnology have been used to add therapeutic efficacy to cancer treatment over the past years. Nonetheless, the clinical translation of nanomedicine continues to have a very poor success rate [20]. The ineffective intratumoral penetration of the DDSs, which is mostly brought on by the tumor microenvironment's (TME) high interstitial fluid pressure, stroma abundance, and inadequate blood supply, is a major contributing factor to this poor conversion [21, 22].

This paper offers a comprehensive overview of the composition and classifications of dendrimers, the process of synthesizing dendrimers, and their utilization in nanomedicine, particularly in drug administration. Furthermore, this review describes the process of creating uniform metallic nanoparticles using PAMAM dendrimers and explores their usefulness in enhancing the delivery. Delves into the complexities of dendrimer synthesis, emphasizing the challenges and costs associated with production.

2. Properties of dendrimers

Dendritic structures receive recognition for their extraordinary precision in terms of architecture. Dendrimers and Dendron stand out as monodisperse, highly symmetrical, Compounds with a spherical structure [23]. Dendritic molecules can be broadly classified into two groups based on molecular weight, with their domain falling within these rejuvenated categories. The first encompasses low-molecular-weight species like dendrimers and dendrons, while the second comprises higher-molecular weight varieties Instances comprise dendronized polymers, hyperbranched polymers, and polymer brushes, among others [24].

Dendrimers exhibit their primary characteristics largely determined by the functional groups decorating their molecular surfaces. However, it is noteworthy that dendrimers with internal functionality are also observed in certain instances [25-27]. This structural feature allows for the encapsulation of functional molecules, effectively isolating active sites and mimicking the architecture found in biomaterials [28-30]. Moreover, dendrimers can be tailored for water solubility, a characteristic uncommon in the majority of polymers. This is achieved by altering their outer shell through the incorporation of charged components or other hydrophilic groups. Dendrimers possess controllable attributes, including aspects such as toxicity, crystallinity, the formation of to-dendrimers, and Stereochemistry [31].

Dendrimers are categorized based on their generation, reflecting the number of iterative branching cycles they experience throughout the synthesis process. For instance, in the case of a dendrimer synthesized through a convergent method with three rounds of branching reactions on the core molecule. It is classified as a dendrimer of the third generation. Each subsequent iteration results in the creation of a dendrimer with a molecular weight approximately twice that of its precursor. Dendrimers of advanced generations provide an increased abundance of functional groups exposed on their surfaces, allowing for more precise customization to suit specific applications [32]. Some important properties of dendrimers are given in (Figure 1).

Due to their distinct nanoscale characteristics, dendrimers are important in drug delivery systems and have an impact on whether they are categorized as biologics or novel chemical entities. Their precise dimensions, form, and surface properties enable customized drug delivery, increasing therapeutic effectiveness and reducing adverse effects. These elements are covered in more detail in these sections regarding unique structural properties for instance size and shape, Unlike linear polymers, dendrimers have a hyperbranched globular shape that gives them exact control over their molecular weight and size[33]. Additionally, Surface Function and targeting moieties can bind to their tunable surface chemistry, allowing for site-specific drug delivery and controlled release[34, 35]. In terms of applications of drug delivery for example versatility of both hydrophilic and hydrophobic medications can be en-

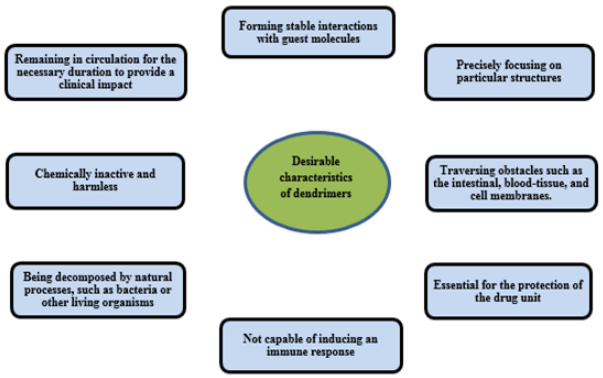

Fig. 1. Essential attributes of dendrimers.

capsulated by dendrimers, increasing their solubility and stability-two essential components of an efficient treatment[34, 36]. And also they can control release kinetics and shield medications from deterioration, making them very useful in the treatment of cancer[36, 37]. Although dendrimers show promise for drug delivery, regulatory viewpoints on their synthesis, safety, and biocompatibility all of which are still major development challengemay determine whether they are classified as new chemical entities or biologics[33, 34].

3. Structure and types of dendrimers

3.1. Structure

A typical dendrimer mostly comprises four major components including an initiator core with one or more reactive groups to which the dendrons are connected, interior layers or shells made up of repeating branched units that are attached to the initiator core, with each layer representing a generation, terminal functional groups located at the ends of the nanostructure, which determine the nature and drug entrapping ability of the dendrimer, and void spaces [10] are shown in (Figure 2).

3.2. Types of Dendrimers

Dendrimers are a class of complex, synthetic polymers that have unique structural and functional properties. These creatures display a unique and complex structure, with several branches that emanate from a core center [31]. Dendrimers have been utilized in several domains including medication delivery, imaging, catalysis, and nanotechnology owing to their adjustable dimensions,

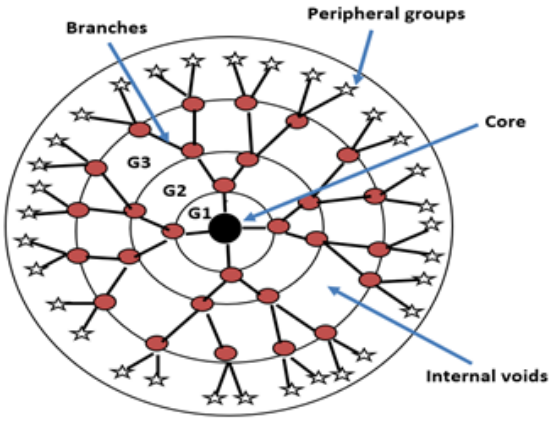

Fig. 2. The constituents of a dendrimer structural unit.

Table 1. Applications of different types of dendrimers in drug delivery

NO.	Types of Dendrimers	Applications in drug delivery	References
1	Poly (amidoamine) PAMAM	Studies have demonstrated that PAMAM dendrimers have potential applications in drug administration, gene therapy, medical imaging, and diagnostics. Also, PAMAM dendrimers can undergo peripheral modification using polyethylene glycol (PEG) and folic acid (FA) to improve the effectiveness of drug delivery and decrease cytotoxicity.	[39, 40]
2	Poly (propyleneimine) PPI	PPI dendrimers have been employed for the covalent attachment of doxorubicin (DOX), a cytotoxic chemical used in chemotherapy, using an acid-labile linker. This acid-labile release mechanism enables precise medication release in acidic conditions, specifically within tumor cells, rendering them suited for cancer treatment. As well as they have been employed for the encapsulation of the trypanocidal medication benznidazole (BZN). Encapsulating BZN in PPI dendrimers has demonstrated enhanced bioavailability, prolonged release duration, and improved drug administration to damaged tissue.	[41, 42]
3	Poly(ether) dendrimers	Enhancing the solubility of poorly soluble medicines improves their effectiveness in drug delivery applications. Furthermore, active drug release strategies can be employed to create mechanisms that separate medicines from the dendrimer in response to specific stimuli, so enabling enhanced regulation of drug release.	[43]
4	Phosphorus-containing	Phosphorus-containing compounds are frequently developed as prodrugs to enhance their selectivity and bioavailability, minimize side effects and toxicity, or serve as analogs of biomolecules with natural substances and antagonistic endoenzyme supplements. Phosphorus-containing medications can function as prodrugs, serving as inactive precursors of active drugs that undergo chemical or enzymatic transformations within the body to become active.	[44]
5	Silicon-containing	Silicon-containing compounds, such as porous silicon, have garnered considerable interest in the realm of drug delivery because of their distinctive characteristics and possible uses. Porous silicon, specifically, has demonstrated potential as a drug delivery system because of its ability to degrade naturally, its compatibility with living organisms, and its capacity to enclose different therapeutic substances.	[45]

structure, and surface properties [38]. There are many prevalent types of dendrimers, The Most common types are shown in (Table 1).

4. Synthesis of dendrimers

The discovery of dendrimer synthesis was initially documented in 1985 [46]. The synthesis of dendrimers can be accomplished through two primary methods: divergent synthesis and convergent synthesis [47]. Divergent synthesis involves the progressive construction of a dendrimer starting with a multifunctional core molecule. Each reaction step must be executed thoroughly to avoid errors that may result in impurities. Purifying these contaminants is difficult because of the disparity in size between flawless and flawed dendrimers [48]. In contrast, convergent synthesis initiates from the outermost arm of the final dendrimer, using the molecular structure as a starting point. Before each generation, this approach necessitates the synthesis of branches of different sizes, with the eventual generation number set [49]. Dendrimers are distinct nanoscale molecules that possess precisely specified topologies and may be created using controlled techniques, resulting in uniform and structurally controlled macromolecular architectures [50]. The divergent and convergent synthesis methods are two discrete strategies in organic chemistry, each with unique advantages and applications. While divergent synthesis typically entails building complex molecules from a common precursor through a series of branching reactions, convergent synthesis emphasizes assembling larger structures from smaller, pre-synthesized components. The following sections outline the key differences and applications of these methods. In the case of divergent synthesis, The process entails stepwise reactions from a single precursor, permitting the generation of multiple products simultaneously for example, The synthesis of arboridinine and arborisidine used a divergent strategy, using a Michael and Mannich cascade to achieve a branch point[51]. Additionally one Advantage of it is that eases the investigation of various structural modifications and can efficiently lead to various compound libraries[52]. On the other hand, the convergent synthesis process includes synthesizing smaller fragments independently before merging them to form a larger molecule. For instance, The synthesis of the H2B protein confirmed that convergent strategies yield higher purity and efficiency compared to one-pot methods[53]. Moreover Simplifies purification processes due to the greater dissimilarity between products and side products. Therefore, divergent synthesis excels in generating diverse compounds from a single precursor, convergent synthesis is often a favorite for complex targets due to its efficacy and effortlessness of purification. Ultimately, the choice between these methods eventually depends on the specific goals and requirements of the synthesis project[52].

4.1. Schematic of divergent synthesis of dendrimers

In divergent approaches, the synthesis of dendrimers commences with a multifunctional core (Figure 3). Subsequently, the dendrimer expands outward in a stepwise fashion through a series of reactions, frequently incorporating Michael's reactions. Achieving complete fruition at every phase of the reaction is imperative to prevent inaccuracies in the dendrimer structure, thereby averting potential discrepancies in branch lengths resulting in trailing generations. The presence of impurities has the potential to undermine the dendrimer's functionality and disrupt its symmetry. However, purging them out is exceptionally challenging due to the minimal size difference between perfect and imperfect dendrimers [32].

4.2. Schematic of convergent synthesis of dendrimers

Convergent methods involve the construction of dendrimers by assembling small molecules, ultimately resulting in their placement on the surface of the spherical structure (Figure 4). The responses advance towards the center, gradually forming connections to a central core. This approach facilitates the removal of impurities and shorter branches during the synthesis process, resulting in a more uniform final dendrimer. However, dendrimers produced through this method tend to be smaller compared to those generated through divergent methods, primarily due to the constraining influence of steric effects around the core, which leads to crowding [54, 55].

5. Mechanism of drug–dendrimer interactions

5.1. Physical encapsulation of dendrimers

The process of incorporating complex macromolecules with clearly defined structures, known as dendrimers, into another substance or structure is known as physical encapsulation. Encapsulation can occur in liposomes, polymers, or other nanostructures [56]. Dendrimers have special properties that make them useful as carriers of genes, medications, or other therapeutic agents. These characteristics include their high surface functionality and precise molecular architecture [57, 58]. The confinement of dendrimers within the structure of another substance is referred to as physical encapsulation. This approach improves the dendrimers' compatibility with biological systems, controls their release rate, and shields them, among other advantages [59].

5.2. Electrostatic interactions of dendrimers

Dendrimers, complex polymers having a highly branched structure, are known for unique properties like their ability to engage in electrostatic interactions. The attraction or repulsion of charged groups inside the dendrimer's structure or between the dendrimer and its sur-

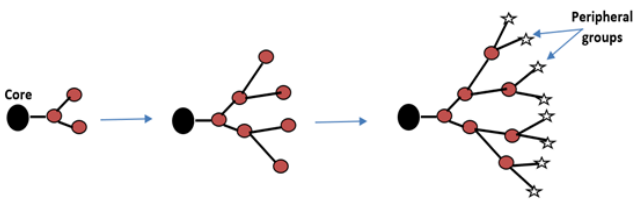

Fig. 3. Synthesized of dendrimers by a divergent synthesis pathway.

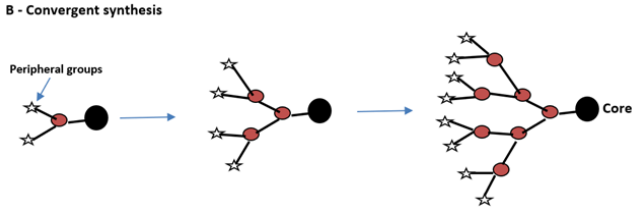

Fig. 4. Convergent synthesis approach for dendrimers.

roundings is the primary cause of the electrostatic interactions in dendrimers. Such interactions have a significant effect on dendrimer production, stability, and applications [60].

5.3. Covalent conjugation of dendrimers

Covalent conjugation of dendrimers is the process by which functional groups or molecules are bonded to the branches or surface of dendrimers via covalent chemical bonds (Figure 5). Researchers can customize dendrimers for specific purposes by utilizing covalent conjugation to incorporate features like targeting ligands, imaging agents, medicines, or other biomolecules [43]. The process of regulated functionalization is essential for improving the characteristics and effectiveness of dendrimers in multiple domains such as medication delivery, diagnostics, materials science, and nanotechnology [61].

6. Applications of dendrimers

Dendrimers find diverse applications by attaching various chemical entities onto their surface, they demonstrate remarkable versatility, functioning as highly efficient detection agents in various applications, encompassing dye molecules, affinity ligands, targeting components, radio ligands, imaging agents, and pharmaceutically active compounds, among others. The exceptional flexibility of dendrimers arises from their multivalent structure, providing a multitude of binding sites for active species. Researchers have strived to harness the hydrophobic conditions within dendritic media to enhance photochemical reactions [62-64]. This approach facilitates the synthesis of products that would pose challenges using alternative methods. To this end, water-soluble dendrimers terminated with carboxylic acid and phenol groups were synthesized, demonstrating their efficacy in drug delivery and facilitating chemical reactions within their interiors [65]. This potential breakthrough could enable researchers to affix both targeting molecules and drug compounds onto a single dendrimer. This innovative approach holds the promise of minimizing adverse effects on healthy cells caused by medications [66, 67].

Dendrimers also serve as effective solubilizing agents. Since its emergence in the mid-1980s, the distinctive dendrimer architecture consistently garners recognition as a prominent choice within the domain of host-guest chemistry [68]. Furthermore featuring a hydrophobic core and a hydrophilic periphery demonstrate characteristics reminiscent of micelles, showcasing container-like properties when they are dissolved in a solution [69]. Newkome proposed the idea of employing dendrimers as unimolecular micelles in 1985 [70]. This juxtaposition emphasizes the efficacy of dendrimers in their role as dissolving agents [71][36]. A significant proportion of pharmaceutical drugs in the industry tend to be hydrophobic, presenting a notable challenge in formulation. However, dendrimeric structures offer a solution by enabling the encapsulation and solubilization of these drugs, Due to their capacity to form substantial hydrogen bonds with water, they can effectively interact with it [72-74]. Scientists in dendrimer laboratories are actively engaged in refining the solubilizing properties of dendrimers, to advance their applications in drug delivery [75, 76] and in the targeting of specific carriers [77-79].

To find application in pharmaceuticals, dendrimers must successfully navigate regulatory approval processes. One promising dendrimer framework tailored for this application, which offers potential advantages, is the polyethoxyethylglycinamide (PEE-G) dendrimer [80]. Several investigations have confirmed the heightened HPLC purity, stability, solubility in aqueous environments, and minimal intrinsic toxicity of the framework [81, 82].

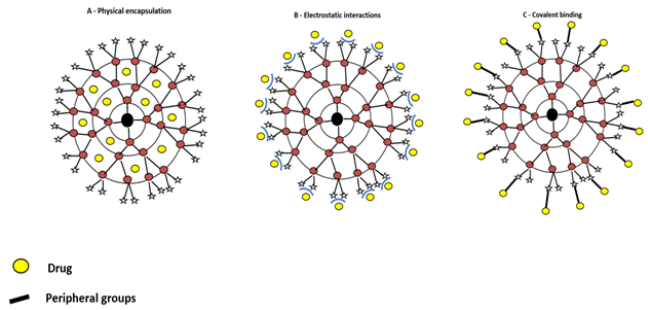

Fig. 5. Illustration depicting the three processes by which drugs interact with dendrimers.

7. Drug delivery

Considerable interest has been garnered by various approaches aimed at delivering unaltered natural products utilizing polymeric carriers. Considerable attention has been drawn to dendrimers because of their thorough exploration of encapsulating hydrophobic compounds and enabling the effective delivery of anticancer medications [83]. Dendrimers exhibit distinctive attributes such as uniform size, solubility in water, efficient encapsulation capabilities, and a wide range of customizable peripheral groups [10, 15, 84]. These qualities render dendrimers exceptionally well-suited for serving as carriers in drug delivery applications [85-88].

7.1. The impact of dendrimer chemical modifications on drug delivery

Dendrimers shine as drug delivery platforms due to their extensive customization options. With a vast array of chemical modifications at their disposal, scientists can fine-tune their compatibility with the body and deliver drugs precisely to the desired. Drugs can be linked to dendrimers through several methods, such as creating a dendrimer prodrug via covalent bonding or external surface conjugation, establishing ionic coordination by incorporating outer functional groups with charged entities or encapsulating a drug within a micelle-like structure formed by the supramolecular assembly of dendrimer and drug [89, 90].

Within the framework of a dendrimer prodrug structure, the connection between a drug and a dendrimer can take place via direct bonding or a process facilitated by a linker. The choice depends on the desired release kinetics for the targeted effect. This linker could exhibit responsiveness to pH, undergo enzymatic catalysis, or incorporate a disulfide bridge. Dendrimers offer a myriad of possibilities for linker chemistries due to the diverse array of terminal functional groups they encompass. This feature adds a dimension of customization to the system, opening up numerous opportunities for tailored applications. Key considerations in linker chemistry encompass assessing the release mechanism upon arrival at the designated site, whether within a cell or a specific organ system, ensuring

an optimal drug-dendrimer spacing to prevent lipophilic drugs from undergoing folding into the dendrimer and evaluating the degradability of the linker, along with possible modifications to the drugs post-release [91, 92].

Polyethylene glycol (PEG) is extensively utilized as a modification approach for dendrimers, primarily aimed at modifying their surface charge and extending their circulation duration [92]. The interaction of dendrimers with biological systems is significantly influenced by the surface charge they carry. Notably, dendrimers equipped with amine termini often engage with cell membranes characterized by anionic charges. In vivo studies have indicated that polycationic dendrimers, in particular, may manifest cytotoxic effects by inducing membrane permeabilization. The reduction of this occurrence can be partially addressed by incorporating PEGylation caps into amine groups. This modification leads to a decrease in cytotoxicity and reduced hemolysis of red blood cells [93]. Furthermore, the results of the research suggest that incorporating PEGylation into dendrimers enhances drug loading, delays drug release, prolongs circulation times in vivo, and reduces toxicity in comparison to dendrimers without PEG modifications [94].

Numerous targeting ligands have been utilized to customize the biodistribution of dendrimers, facilitating precise delivery to particular organs. A promising route for targeted drug administration is provided by the increased expression of folate receptors in tumor cells. Additionally, conjugating folic acid to PAMAM dendrimers has been demonstrated to enhance targeting capacities and decrease off-target toxicity. In mouse cancer models, this improvement is coupled with the maintenance of on-target cytotoxicity for medications like methotrexate [95, 96]. The application of antibodies to steer dendrimers toward particular cellular targets has shown promise for targeted medication administration. Because brain cancers have higher levels of expression of Epidermal Growth Factor Receptors (EGFRs), they are a useful target for precisely applying medication. Rats were used as delivery systems to introduce boron to cancer cells in a novel way. Combining a boronated dendrimer with a specially tailored monoclonal antibody that targets EGFRs allowed for this discovery, which marks a ground-breaking development in the field of cancer treatment research. This accomplishment represents a significant turning point in neutron capture treatment, offering a novel approach to the fight against cancer [97].

The insertion of peptides into nanoparticle dendrimers has demonstrated encouraging potential in the accurate targeting and elimination of colorectal (HCT-116) cancer cells in co-culture settings. Targeting peptides have been successfully used to deliver drugs precisely to certain cells or locations. Combining these peptides with dendrimers has been observed to enhance targeting specificity. Notably, the unique dendrimer nanoparticle, gemcitabine-loaded YIGSR-CMCht/PAMAM, induces targeted mortality in colorectal cancer cells through selective interaction with laminin receptors. Peptide dendrimers present a promising avenue for the precise targeting of cancer cells and the delivery of chemotherapeutic agents in future applications [98].

Furthermore, the precise adjustment of dendrimers' cellular internalization mechanism can be achieved through chemical targeting modifications. Absorbed through fluid-phase endocytosis, activated microglia readily take up the unaltered PAMAM-G4 dendrimer in its natural state. On the flip side, introducing mannose modifications into hydroxyl-functionalized PAMAM-G4 dendrimers has been shown to alter the internalization mechanism. This modification tends to promote endocytosis through the mannose receptor (CD206), suggesting a shift in the internalization process. The incorporation of mannose modification has been associated with alterations in biodistribution patterns in rabbit models, as indicated by observable alterations across the entire body [99].

7.2. Pharmacodynamics and pharmacokinetics

Dendrimers possess the capacity to alter the pharmacokinetic and pharmacodynamic (PK/PD) traits of a pharmaceutical compound, potentially ushering in a new era. As carriers, they shift the focus from the drug's inherent properties to variables Similar to dendrimer localization, mechanisms of drug release, and excretion of dendrimers. Thereby exerting a significant influence on the overall PK/PD profile. The modulation of ADME properties can be achieved through precise adjustments to dendrimer size, structure, and surface characteristics [100]. Modifying the dimensions and arrangement of G9 dendrimers can induce a discernible change in biodistribution, manifesting a distinct inclination towards the liver and spleen. On the flip side, G6 dendrimers tend to disperse more extensively, and an increase in molecular weight correlates with decreased rates of urinary and plasma clearance. Consequently, this alteration contributes to an extension of the terminal half-life, as highlighted in the literature [101].

7.3. Routes of delivery

To enhance adherence to prescribed treatments, oral drug delivery is frequently favored over other administration routes. Nevertheless, the oral bioavailability of numerous drugs is often quite limited. Dendrimers present a promising solution by enhancing the solubility and stability of drugs administered orally. This, in turn, facilitates improved penetration through the intestinal membrane [102]. In mouse-based studies, research delved into the bioavailability of PAMAM dendrimers when coupled with a chemotherapeutic agent. The findings revealed that approximately 9% of dendrimers administered orally retained their structural integrity during circulation, exhibiting minimal degradation within the gastrointestinal tract [103].

The potential and promise of employing intravenous dendrimer delivery as gene vectors for transporting genes to diverse organs, including tumors, are considerable. A research study revealed that the intravenous administration of a blend of PPI dendrimers and gene complexes led to the activation of genes within the liver. Furthermore, a separate investigation illustrated that the introduction of a similar injection resulted in the reduction of tumor growth in the observed animal subjects [104, 105].

The main difficulty in transdermal drug delivery is linked to the challenges posed by the epidermis. Medications with hydrophobic properties face considerable challenges when attempting to penetrate the skin layer due to their tendency to be tightly associated with skin oils, impeding effective permeation. In recent times, PAMAM dendrimers have surfaced as proficient carriers for NSAIDs, augmenting their hydrophilicity and consequently facili-

tating enhanced penetration of the drugs to deeper tissue layers [106, 107]. These modifications function as polymeric agents that enhance transdermal delivery, promoting more seamless penetration of drugs through the skin barrier [108].

Dendrimers have emerged as potential novel carriers for ophthalmic drug delivery, offering a distinct approach from the currently employed polymers to achieve this objective. Vanndamme and Bobeck undertook a research investigation utilizing PAMAM dendrimers as vehicles for transporting drugs to the ocular region of rabbits. The research aimed to assess the effectiveness of these dendrimers using two model drugs. The residence time of this delivery technique within the eye was found to be comparable, and in certain cases, even longer than the period attained with currently used bioadhesive polymers in ocular delivery. The findings suggest that medications administered using dendrimers exhibited improved effectiveness and increased availability in comparison to their counterparts in a drug-free state [109, 110]. In addition, corneal sutures have utilized photo-curable hydrogels made from dendrimer-hyaluronic acid, which are specifically engineered to enhance drug-release capabilities. These are directly administered to the eye for maximum efficacy. The hydrogel sutures demonstrated remarkable efficacy in rabbit models, surpassing conventional sutures as medical devices. Concurrently, they exhibited a noteworthy decrease in corneal scarring, as confirmed by other investigations [110].

7.4. Brain drug delivery

Dendrimers offer substantial potential for drug delivery by addressing longstanding challenges in this field. Particularly in the domain of delivering drugs to the brain, dendrimers capitalize on the Enhanced Permeability and Retention (EPR) effect, strategically navigating through the impediments presented by the blood-brain barrier (BBB) for efficient in vivo delivery. One example of how they might efficiently target specific locations is the natural affinity that hydroxyl-terminated PAMAM dendrimers have for inflammatory macrophages in the brain. Using fluorescently labeled dendrimers in an experimental rabbit cerebral palsy model has proven this characteristic [111]. The ability to administer pharmaceuticals accurately has proven to be crucial in the efficient transportation of medications for a wide variety of illnesses. This includes a variety of illnesses, including cerebrovascular accidents, various neuroinflammatory diseases, traumatic brain injury, and hypothermic circulatory arrest episodes. A wide range of animal models, including mice, rabbits, and dogs, have been used in these studies [112]. The degree of inflammation and disruption of the blood-brain barrier (BBB) are directly related to the entry of dendrimers into the brain. The degree of BBB damage is the primary factor that facilitates dendrimer penetration [113]. The location largely favors activated microglia. Furthermore, N-acetyl cysteine conjugated with dendrimers has been shown to exhibit remarkable anti-inflammatory efficacy in in-vivo studies, demonstrating efficacy at doses more than 1000 times lower than those needed for the unbound medication. The effectiveness of this approach has been demonstrated in the reversal of phenotypes associated with several inflammatory conditions, some instances comprise disorders such as cerebral palsy, Rett syndrome, macular degeneration, and a multitude of other conditions [111].

7.5. Gene delivery and transfection

Effectively delivering DNA fragments to specific cellular locations presents numerous challenges. Continuing investigations seek to exploit dendrimers for transporting genes into cells, ensuring the preservation and functionality of DNA without compromise or deactivation. To ensure the resilience of DNA in the face of dehydration, complexes formed by dendrimers and DNA were enveloped within a water-soluble polymer. These encapsulated complexes were then strategically incorporated into or nestled between functional polymer films known for their swift degradation, thereby enhancing the efficiency of gene transfection. Building upon this approach, PAMAM dendrimer/DNA complexes for the encapsulation of biodegradable polymer films endowed with functional attributes, thereby enabling substrate-mediated gene delivery. Studies suggest that the swiftly declining functional polymer exhibits substantial promise in the realm of targeted transfection, as highlighted in various studies [114, 115]. In gene therapy, dendrimers have become adaptable nanocarriers that provide creative ways to safely and efficiently transfer genetic material. Their distinct branching topologies allow for alterations that improve biocompatibility and targeting, making them suitable for a range of therapeutic applications, especially the treatment of cancer and neurological illnesses. The significant uses of dendrimers in gene therapy are in these sections . In terms of gene delivery mechanisms effective gene delivery depends on dendrimers' ability to encapsulate DNA and RNA and protect them from enzymatic destruction while in circulation[116]. Furthermore They aid in the passage of therapeutic siRNA over the blood-brain barrier (BBB), resolving a major obstacle in the treatment of illnesses of the central nervous system[117]. In the case of targeted therapy, targeting ligands can be added to functionalized dendrimers to increase their specificity for tumor cells and lessen damage to healthy tissues[118]. Additionally, Their capacity to provide several therapeutic substances at once supports combination therapies, increasing the effectiveness of treatment[119]. Compared to advantages over traditional vectors dendrimers were safer substitutes for viral vectors for gene delivery because they were more flexible and less immunogenic, Moreover, Their high solubility and nanoscale size improve bioavailability and therapeutic results[120]. Despite, The translation of dendrimers into clinical practice for gene therapy faces several significant challenges, despite their promising potential as drug delivery systems. These challenges primarily revolve around biocompatibility, toxicity, regulatory hurdles, and the need for scalable synthesis methods. In terms of biocompatibility and toxicity, due to their frequent lack of biocompatibility, dendrimers may be harmful to biological systems. Thus, to reduce negative effects, it is essential to comprehend dendrimer biodistribution and clearance mechanisms. Regarding Regulatory challenges dendrimer-based therapy regulations are complicated and only a small number of medicines have been approved for clinical usage[120, 121]. Due to the unique nature of dendrimer technology, regulatory authorities require comprehensive safety and efficacy data, which can be challenging to collect[122]. As for Synthesis and Scalability, The current techniques for dendrimer production are frequently neither reproducible

nor scalable, which makes it difficult to use them practically in clinical settings. Therefore, To create dendrimers in large enough quantities for clinical trials, synthesis processes must be innovative. Even while dendrimers have a lot of potential for gene therapy, these issues nevertheless restrict their practical use[34].

7.6. Sensors

Dendrimers exhibit significant promise within the realm of sensors, with explored applications encompassing a diverse range of systems. Such as those utilizing poly(propylene imine) for proton or pH sensing [123]. The application of composites involving cadmium-sulfide/polypropylenimine tetrahexacontaamine dendrimers for the detection of fluorescence signal quenching [124]. The application of poly(propylenamine) dendrimers from both first and second generations in the realm of photodetection for metal cations has been pursued [125]. Exploration in this field is continually advancing through various methodologies, driven by the prospect of uncovering numerous detection and binding sites within dendritic structures, a surge of motivation propels exploration.

7.7. Nanoparticles

Dendrimers have been employed in creating consistent metallic nanoparticles through the fabrication process, showcasing their effectiveness among diverse methodologies. One notable example is PAMAM, which demonstrates significant utility in this context, Dendrimers demonstrate practical functionality through the strategic placement of tertiary amine groups at the branching nodes within their structural framework. When immersed in a dendrimer solution containing water, metal ions intricately engage with the lone pair of electrons situated at the tertiary amines present within the solution. Following the completion of the complexation process, the ions undergo reduction to achieve their zerovalent states. This leads to the creation of nanoparticles enclosed within the dendrimer structure, with the dendrimer-encapsulated nanoparticles demonstrating a width spanning from 1.5 to 10 nanometers [126].

7.8. Other applications

Dendrimers are being increasingly utilized by companies to enhance the efficacy of agrochemical delivery in modern agriculture, where pesticides, herbicides, and insecticides are widely employed. This utilization of dendrimers aims to promote more resilient plant growth and actively contribute to combatting plant diseases [127]. Moreover, dendrimers are currently undergoing thorough exploration due to their potential application as substitutes for blood. The substantial reduction in degradation rates, in comparison to free heme, is attributed to the steric bulk surrounding a heme-mimetic center [128, 129]. Reducing and effectively managing the cytotoxic effects associated with free heme. The creation of core-shell structures, such as microcapsules, is based critically on the use of the dendritic functional polymer (PAMAM). This polymer is vital for the manufacturing of self-healing coatings made of a diversity of materials, including either traditional or non-conventional ones [84] as long as those come from renewable sources [130].

8. Conclusion

Dendrimers as drug delivery vehicles are a tough field, but this thorough research makes an easy way to clarify things. Drug delivery is done successfully by dendrimers, which are differentiated by their well-structured branching structure. They are greatly accurate structurally, which provides for a precise take of their properties. They should be tailored for different applications, including the delivery of medications, the transfer of genes, and the development of sensors. They have been made using a variety of methods, and their various characteristics and potential applications have all been checked. Dendrimers have been verified to raise the solubility and stability of pharmaceuticals, permitting to development of drug delivery via oral, intravenous, transdermal, and ocular routes. They have a very much promise for directly administering medication to the brain, specifically an example of neuroinflammatory illnesses. Also, dendrimers have been investigated for their function in transfection and gene delivery, which makes it more facile to successfully transport DNA into cells. In addition, dendrimers have furnished evidence in the fields of sensors, nanoparticle synthesis, and agricultural chemical delivery. Their application in the manufacture of self-repairing coatings and as blood substitutes shows chances for different applications. The developing significance of dendrimers in the pharmaceutical and medical fields is demonstrated by continuous research and clinical investigations. As dendrimers improve and obtain new applications, they can transform gene therapy, medicine delivery, and other scientific and medical fields. They have very dynamic and amazing properties as drug delivery vehicles, with numerous avenues for innovation and substantial effects. Drug delivery methods could be greatly advanced by dendrimer technology, especially when it comes to treating complex illnesses like cancer and neurological diseases. To optimize therapeutic efficacy, future research should concentrate on increasing dendrimer design, drug encapsulation, and biocompatibility. In terms of key areas of research, for instance, in cancer treatment, dendrimers can be designed to deliver chemotherapeutic drugs to tumor cells in a targeted manner, improving drug bioavailability and lowering systemic toxicity.

Conflict of interests

The authors declare that they have no conflicts of interest.
-In this manuscript, all tables have been authored by us.
-The authors signed the ethical consideration's approval.
-Ethical clearance: our work has been approved by the scientific and ethical committee at the Sulaimani Polytechnic University (SPU).

Consent for publications

All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

No humans or animals were used in the present research.

Informed consent

The authors declare that no patients were used in this study.
Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contribution statement

All authors of this study participated equally in all stages of the writing process; they also reviewed and approved the submission of this work.

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