Original Article

Recent Progress, Therapeutic Concepts And Pharmaceutical Challenges Of Dendrimer Based Drug Delivery System

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Abstract

Nanoscale size, a multi-functionalized surface, high branching, a cavernous interior, and other distinctive structural features of dendrimers make them perfect drug delivery systems. In the past forty years, dendrimer research has expanded tremendously from synthesis to use since Fritz Vögtle originally published the first dendrimer in 1978. Nanoscale size, a multi-functionalized surface, high branching, a cavernous interior, and other distinctive structural features of dendrimers make them perfect drug delivery systems. This review focuses on the most recent advancements in the use of dendrimers as drug and gene carriers, including active drug release strategies to release the drug or gene from the dendrimer in response to stimuli, size-adaptive and charge-reversal dendrimer delivery systems that can better utilise the size and surface characteristics of dendrimer bulk and micro/nano dendrimer gel delivery systems, and other recent developments. Recent developments in dendrimer formulations may result in the creation of novel gene and drug products as well as combination medicines.

KEYWORDS: PAMAM, dendrimer, multifunctional, solubility, stability, targeting, transdermal.

INTRODUCTION

History of Dendrimer

The Greek word "dendron," which signifies tree, meros, or branch, is the source of the word "dendrimer" [1]. The first "cascade" and "nonskid-chain-like" molecules with molecular cavity topologies were created and published by Buhleir and colleagues in 1978. These molecules were eventually identified as the earliest types of dendritic polymers [2]. The Dow Laboratories' Donald A. Tomalia and his colleagues made a significant advancement in the creation of dendrimers between 1979 and 1985 [3]. They created what Tomalia dubbed dendrimers, which are polymers with a hollow central core and tendrils that branch outward precisely and predictably. The early development of dendrimers was influenced by these two scientific communities. More than 100 dendritic structures have been described thus far, with polyamidoamine (PAMAM) dendrimers, polypropyleneimine (PPI) dendrimers, as well as dendrimers based on polyamide, polyether, polyester, and phosphorus, being some of the more widely known dendritic families [5]. Additionally, numerous new dendrimers with the efficient synthesis process and structure diversity have developed as a result of the development of diverse synthetic techniques, including efficient orthogonal click chemistry and multicomponent reaction (MCR) [6]. The growth of dendrimers and their use in chemistry, materials science, biological research, and medicine have been aided by all the progress. The mono-dispersity, high symmetry, and surface polyvalency of dendrimer set it apart from conventional linear polymers. Dendrimer production involved numerous growth processes, which increased branching and generation levels until a three-dimensional spherical structure was formed [7]. Dendrimer has a specific core-shell architecture and restricted polydispersity due to the unique synthetic technique [1]. Dendrimer properties like as size, surface charge, peripheral functional groups, and solubility may also be influenced by the synthesis process [1]. For example, dendrimers from higher generations have larger sizes, greater inner cavities, and more terminal functional groups. Electrophoretic and mass spectroscopy measurements have been developed to detect the mono-dispersity features and the effective charge of dendrimers in addition to the standard analytical techniques such as nuclear magnetic resonance (NMR), gel permeation chromatography (GPC), dynamic light scattering (DLS), high-performance liquid chromatography (HPLC), etc. [8]. Rekha and Sharma claim that, generally speaking, in pharmaceutics, medications that have trouble exerting their pharmacological effects can be combined with carriers or conjugated with another medication to enhance the overall effect. Due to the condition of the cells, targeting specificity is crucial, particularly in cancer therapy. For instance, chemotherapeutic medicines work better when delivered via a nano-carrier because they can more precisely target particular cells or places while avoiding normal cells, which may serve as possible targets if the nanomaterial weren't there. A variety of CNS illnesses can today be treated using both invasive and non-invasive methods, with the latter being considered safer and more affordable than a high-risk invasive surgery [9]. Nanoparticles (NPs), which fall under the larger category of colloidal drug carriers, are the most often used nanomaterial in neurodegenerative illnesses when using non-invasive techniques [10]. De Marco recently examined the use of supercritical fluid technologies to create NPs. Since PD is the subject of this review, research is being done to determine which nanomaterial is compatible with the disease and most effective at treating its symptoms. Dendrimers, immunoliposomes, and nanoparticles are a few examples of nanomaterials. Good-branched molecules with a distinct 3D structure and limited dispersion yet high performance are called dendrimers [11]. It is generally known that dendrimers have the ability to load substantial amounts of medicines and deliver them to biological membranes via endocytosis. Many drug studies of conjugation to dendrimer were discovered in 2002, however the majority of those studies were focused on the treatment of cancer. Dendrimers can basically be divided into generations. Because of the amine functional core, these generations change with time. The types of dendrimers that have been used or could be used for Parkinson's disease are the only ones covered in this review. First, a polyamidoamine dendrimer, also known as a PAMAM dendrimer, experiences a reaction with methyl acrylate known as a Michael addition. Each amine group produces two half-generation branches after addition that have ester terminations. A full generation will then be attained as the procedure continues in a cycle of amidation, resulting in the creation of numerous additional dendrimer generations. Due to a constant synthesis and manufacture of newer generations after generations, this mechanism explains the "generational synthesis" of dendrimers. The PAMAM dendrimer's drug delivery system for antibacterial, antioxidant, and antiviral medications is widely utilised [12]. Second, the most well-known dendrimer in terms of commerce is polypropyleneimine, or PPI. Since the amine terminal components of this can increase the solubility of the encapsulated drug(s), it is typically used for hydrophobic medicines. However, because of its cationic surface, it induces cell lysis, necessitating "pegylation," or the addition of polyethylene glycol (PEG). Numerous modifications have been made to PPI dendrimer to address its drawbacks because of its capacity to cause cell harm [13].

Architectural Concepts

It is possible to visualise dendritic molecules by seeing the recurrent layering of multifunctional building blocks based on a protection and deprotection scheme or by imagining the addition of progressively more linear, complimentary monomers [14]. This typically produces a branching, tree- or fractal-like molecular motif, where each layer that is included serves as a base for the following layer. A "mushrooming" framework is created because the quantity of reactive sites and branching centres rises with each layer. The attachment of a generic branching building block, which has three reactive sites distinct from the fourth, can be used to depict the synthetic technique [15]. The new monomer has the same functional group properties as the starting materials, with the exception that the perimeter has now developed and expanded to a branched construct, as a result of treating monomer with three equivalents of a like monomer. Two general ways of construction have emerged from the iterative dendritic method. The convergent route, established in 1990 by Fre'chet et al., results in development from the "outside inward," and the divergent route, first proposed by Vogtle et al., where molecular growth effectively proceeds from the "inside outward." Differences between the two approaches result from how the building blocks are added and can be influenced by how functional groups are activated and deactivated [16]. So, in dendritic chemistry, rational protection-deprotection strategy selections developed from classical synthetic chemicals are of utmost significance. A developing specie will produce a progressively larger branched construct when nine equivalents of a triprotected monomer are added to its surface. By flipping the procedure, three equivalents of the higher-order, branching monomer can be added to the simple monomer to create the identical substance. Both approaches enable the creation of dendritic material and each has advantages and disadvantages of its own [17]. Divergent synthesis, for instance, necessitates an ever-increasing number of monomer attachment reactions, which increases the likelihood of incomplete reactions at the ever-expanding periphery, leading to an increased number of imperfections; conversely, convergent synthesis increases the likelihood of producing perfect structures because there are fewer reactions needed to build layers, albeit at lower molecular weights. As a multifunctional monomer grows and its associated steric hindrance increases, it becomes harder to locate and link at a single site. Divergent and convergent approaches have been compared to polymer and organic syntheses, respectively, based on these characteristics and a thorough mass spectrometry investigation by Meijer et al. [18].

PAMAM Dendrimers

PAMAM dendrimers are the most distributed and investigated dendrimers, because their synthesis process is not so complicated and standard dendrimers are commercialized. The dendrimers can be typically synthesized by the divergent pathway through the two-step process of Michael addition of methylacrylate and of amidation of ethylenediamine [19]. When two-steps are complete, the “generation (G)” of the dendrimers comes up. In the case of PAMAM dendrimers, the defect of terminal groups occurs at more than fourth generation because of the crowded terminal groups. The dendrimers have methylester terminals after the Michael reaction but take carboxylic acid and amine terminals after hydrolysis and amidation reactions, respectively. These terminals of dendrimers are possible to modify into any expected functional groups such as alkyl chains, oligomers, polymers, enzymes, proteins, drugs, and so on. Thus, the physicochemical properties of PAMAM dendrimers including solvophilicity depend on the function of terminal groups. Then these core– shell block dendrimers are termed as “monomolecular polymer micelles” [10]. Meanwhile, star dendrimers with linear polymer terminals resemble “core–corona polymer micelles” [11,12]. When a monoamine compound is a core (focal point) material, a “dendron” is synthesized. Since the dendron has an additional functional species at a focal point besides branches/spacers and terminal groups, the functionality of the dendron increases. The focal point is sometimes used for anchoring dendrons on the target materials: A thiol focal point favorably anchors on gold substrates [12] and a siloxane group is adequate for metal oxide surfaces [13]. Conversely, if terminal groups of the dendron are bound on materials, the focal point can be a functional point. When two dendrons with different (hydrophilic and hydrophobic) terminal groups are combined at focal points by the divergent/convergent joint approach, surface block or Janus-type dendrimers are built [14]. These dendrimers accumulate into bilayers at the liquid–solid interface. There are reports of the synthesis of dendrimers and dendrons with long alkyl (hexyl) chain spacers. PAMAM-type derivatives are synthesized from an azacrown core and a siloxane or hydroxyl focal point through a Michael addition by methylacrylate and an amidation by hexamethylenediamine. The derivatives are more flexible and have larger void volumes to encapsulate guest molecules than PAMAM dendrimers and dendrons. Different types of dendritic polymers are synthesized using dendrons as components: Dendrons can be conjugated with linear polymers. When focal points of PAMAM dendrons are combined with a linear polymer, head-to-tail dendritic polymers are synthesized [15]. These polymers display behaviors of amphiphilic molecules, that is, the decrease of surface tension at critical micelle concentration (CMC), the aggregation to micelles or vesicles above cmc, and the formation of Gibbs monolayer at the air–water interface. Dendrons are combined on a linear polymer as side chains [16]. Then different types of amphiphilic dendritic polymers can be synthesized depending on the combination of a liner polymer and dendron side chains.

Other Dendrimers

This procedure allows the production of the first-, second and fourth-generation poly(L-glutamate) dendrimers and their stereochemical homologs, poly(D-alt-L-glutamate) dendrimers, and moreover enables versatile post functionalization of core and periphery in the dendrimers. PPI dendrimer is another type of biocompatible dendrimer [17]. These dendrimers can be produced from a primary amine core by a repetitive reaction sequence of Michael addition of acrylonitrile followed by heterogeneous hydrogenation of the nitrile end groups to the primary amine end groups with a Raney cobalt catalyst. Head-to-tail dendritic polymers are also synthesized from PPI dendron and a linear polymer [18]. Poly(ethyleneimine) (PEI) dendrimers are a homolog of PPI dendrimers [19]. Different from the synthesis procedure of PPI dendrimers, PEI dendrimers are synthesized by the divergent process from an ethylenediamine core through Michael addition reaction for alkylation and Gabriel amine reaction for producing amine-terminal. Since homologs of poly(alkylamine) dendrimers have spacers of alkyl chain (CH2)n (n ¼ 2, 3), they are more hydrophobic than PAMAM dendrimers. Amino acids are also valuable biocompatible units, and dendritic and dendrigraft (hyperbranched) poly(amino acid)s are synthesized [20]. The synthesis of dendrigraft poly(L-lysine) is carried out by polymerization of N-carboxyanhydride in dimethylformamide or in water. Meanwhile, dendritic poly(Llysine) is prepared as follows. N-t-butoxycarbonyl (Boc)-protected lysine is coupled with hexamethylenediamine by the 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate (HBTU)-1-hydroxybenzotriazol (HOBt) method, and then the deprotection (removing of Boc-groups) is performed by trifluoroacetic acid. For growing up to the upper generation, free amino terminal groups of lower generation dendrimers are utilized for the coupling reaction with N-Boc-protected lysine. Same procedure is applied to the synthesis of dendritic poly (L-ornithine) from an ethylenediamine core using N-Boc-protected ornithine [21]. These materials are useful for biomedical purposes. Poly(ornitine) dendrimers/ dendrons can be synthesized even by a different route. The syntheses of dendrimers and dendrons are got started by reacting an ornitine derivative to a 1,4-diaminobutane dihydrochloride core and an alanine methylester hydrochloride focal point, respectively. Poly(glutamate) dendrimers are prepared via an iterative divergent/convergent binomial synthesis starting from a commercially available. Example of Famotidine loaded PEGylated PPI shown in figure 1.

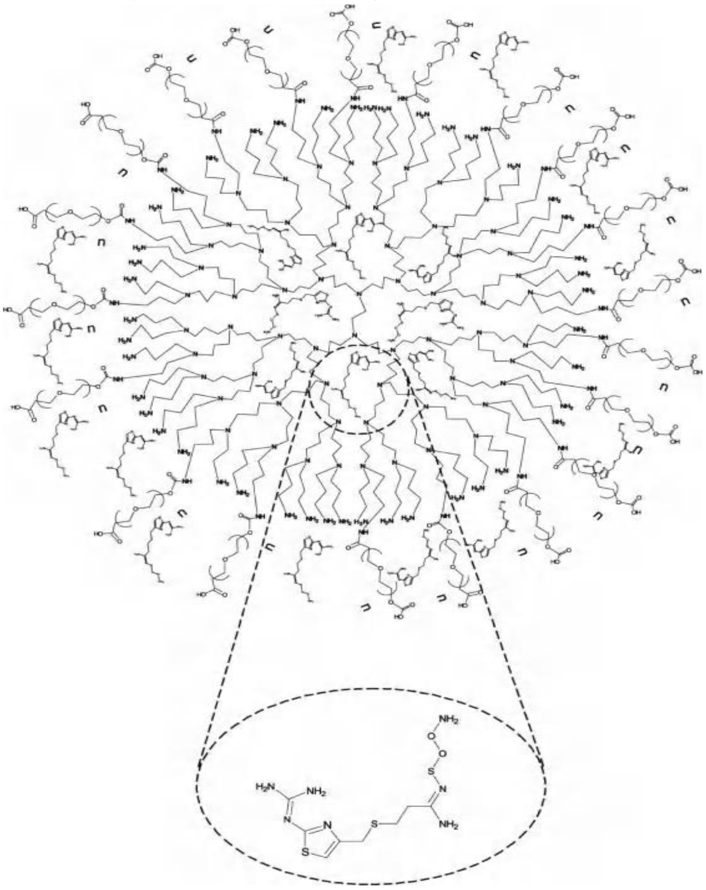

Fig: 1 Famotidine loaded PEGylated PPI 5.0G dendrimer (n 1=4 PEG 2000). (Reprinted, Copyright _ 2009, with permission from Elsevier.)

Dendrimers as drug delivery vehicles

Dendrimers have emerged as an important group of nanostructured carriers for the development of nanomedicine to treat various diseases. Because of structural diversity and adaptability, dendrimers have been used to deliver drugs and genes in many different ways. For instance, dendrimers with a hydrophobic core and a hydrophilic periphery may behave like unimolecular micelles, and they have been utilized to solubilize hydrophobic drugs by entrapping them in the intramolecular cavity [22]. Cationic dendrimers have been extensively applied as non-viral gene carriers. Dendrimer surface groups can be conjugated with drugs and other functional moieties [23]. Conjugating dendrimers with polymers such as polyethylene glycol (PEG), polysaccharide, and polypeptide mainly enhances stability and solubility of the therapeutics to be delivered [24]. PEGylation of dendrimers is a common process through which PEG chains are conjugated to dendrimers, forming a unimolecular micelle. Dendrimer-polysaccharide conjugates are usually adopted to endow the nanomaterials with attractive binding properties and improved compatibility. Polysaccharides, for instance chitosan, hyaluronic acid, cyclodextrin, and dextran have been broadly conjugated to dendrimers. A hyaluronic acid conjugated PAMAM dendrimer showed enhanced tumor penetration property due to the strong affinity of hyaluronic acid to CD44 receptors, which are overexpressed on tumor cells and cancer stem cells. He et al. 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 [25].

GASTROINTESTINAL TRACT

Not all drugs administered orally are meant to address disease of the GIT, in fact, most do not. Although this review discusses dendrimer applications under pharmacotherapeutic headings, we feel that special mention should be made of oral administration for systemic effect. Despite its shortcomings, oral administration remains the preferred route of drug delivery due to ease of ingestion, pain avoidance, versatility, patient compliance, and relatively low cost [26]. Many recent dendrimer studies aim to address the shortcomings of oral drug delivery by improving absorption of poorly soluble drugs or by protecting acid labile drugs, including peptides and proteins, from gastric juices [27]. The development of orally administered drugs, specifically intended for treating pathologies of the colon, has direct pharmacotherapeutic advantages. Diseases of the colon, such as ulcerative colitis, irritable bowel syndrome, and Crohn’s disease, can be treated effectively by administering anti-inflammatory agents to the affected area. Apart from treating local pathologies, the colon is also targeted for the delivery of APIs intended to treat disease elsewhere in the body. The colon offers advantages such as low digestive enzyme activity and high residence time, making colonic delivery useful for administration of peptides and proteins, and also when delayed or prolonged drug absorption is required for treating conditions like asthma, gastric ulcers, or arthritis [28]. A study by Wiwattanapatapee et al. describes the design and synthesis of a water-soluble PAMAM dendrimer conjugate for the colonic delivery) of the topical anti-inflammatory 5-aminosalicylic acid (5-ASA). The dendrimer conjugates were incubated at 37°C with the contents from rat cecum, stomach homogenate, and small intestine homogenate. The drug was only released in significant amounts from dendrimers incubated with cecal contents, indicating that this PAMAM dendrimer can be developed as a carrier for colon-specific drug delivery. The rate of release was much slower than that of the commercial prodrug, sulfasalazine, currently used for 5-ASA delivery.

CARDIOVASCULAR SYSTEM

Nifedipine is a hydrophobic dihydropyridine calcium channel blocker used mainly as an antianginal and antihypertensive [29]. Devarakonda et al. investigated the effect of ethylene diamine core-like PAMAM dendrimers on the solubility of nifedipine and the release of nifedipine suspended in aqueous gels. The correlation between drug release and the increase in solubility, as caused by the dendrimers, was explored. Drug release from aqueous 5% HPMC gels containing nifedipine (2% wt/vol) through 0.2-mm membranes was measured using Enhancer cells and 50% ethanolic solution as the receptor medium. The release from gels containing PAMAM G3 and G5 (0.25%–1% wt/vol) was compared with gels containing the cosolvent isopropyl alcohol (10%–80% vol/vol). It was found that the PAMAM dendrimers significantly increased the rate at which the suspended nifedipine was released from the aqueous gels. The main reason for this was shown to be the increased solubility of nifedipine in the presence of the dendrimers [30].

CENTRAL NERVOUS SYSTEM

Nanoparticles are playing an increasingly important role in the development of brain specific drug delivery systems. Dendrimers, possessing excellent specificity and multifunctionality, are ideal for delivering therapeutic-, diagnostic-, and imaging agents across the blood–brain barrier (BBB) [31]. Venlafaxine is serotonin–norepinephrine reuptake inhibitor (SNRI) used in the treatment of depression and anxiety disorders. Yang and Lopina explored a new drug delivery strategy by loading dendrimer-based venlafaxine carriers into hydrogels. The amount of drug entrapped in a hydrogel usually influences the drug release rate the higher the drug loading, the greater the burst, resulting in a faster release rate. The rate at which this large dendrimeric scaffold diffuses from the hydrogel is assumed to be slower and more controlled than the diffusion of unconjugated drug. It is speculated that the network will protect against excessively fast drug release caused by the actions of enzymes and other biomacromolecules, or that it will at least significantly retard the rate of diffusion [32].

INFECTIONS AND INFESTATIONS

Whilst dendrimers are usually employed as carriers for APIs, some dendrimers have notable therapeutic effects of their own. Naturally occurring sulfated polysaccharides with antiviral activity were reported by Gerber et al. in 1958, and since then many virus inhibiting sulfated polysaccharides have been described [33]. Han et al. synthesized polylysine-dendritic sulfated cellobiose by sulfation of polylysine-dendritic cellobiose. The anti-HIV activity of this compound was assayed in vitro by the MTT method. It was found that the sulfated cellobiose dendrimer has anti-HIV activity as high as that of the antiretroviral zalcitabine, and low cytotoxicty. Because sulfated oligosaccharides have low anti-HIVactivity, it was suggested that the biological activity of the sulfated cellobiose dendrimer was improved by a cluster effect of the sulfated cellobiose that originated from the dendritic structure. Active targeting of HIV drugs and carriers to HIV-infected cells is difficult to achieve, because markers of HIV infection are lacking and latently infected cells do not show signs of infection on their surface. HIV targets only a few cell types and thus targeting should be directed at surface receptors of these cells. An alternative approach is to target cells such as macrophages that act as reservoir sites. These cells are not killed by the disease, allowing the virus to replicate and to continually re-infect the rest of the body [34]. Dutta and Jain achieved some success with this approach. They investigated the targeting potential of mannosylated fifth-generation poly(propylene imine) dendrimers (MPPI) loaded with the nucleoside analog reverse transcriptase inhibitor lamivudine (3TC) [35]. Macrophages have lectin receptors that act as molecular targets for sugar molecules–in this case mannose. The entrapment efficiency of lamivudine-loaded MPPI and poly(propylene imine) dendrimer (PPI) were found to be 43% and 35%, respectively. The in vitro drug release shows that PPI releases the drug by 24 h, and MPPI prolongs the release up to 144 h. The slower release of lamivudine from MPPI indicates its potential as a controlled drug delivery system for the delivery of antiretroviral bioactives. A significant increase in cellular uptake of lamivudine was observed at 48 h: 21 and 8.3 times that of the free drug and PPI complex, respectively. The authors concluded that both PPI and MPPI can improve the safety and efficacy of the anti-HIVagents by reducing their dose and associated adverse effects [36].

PHOSPHORUS DENDRIMERS AS NANO-CARRIERS

Covalent association that necessitates the cleavage for the delivery (A), encapsulation inside dendrimers (B), and electrostatic interactions with the terminal PHOSPHORUS DENDRIMERS AS NANO-CARRIERS Various types of potential uses of dendrimers for drug delivery [37]. Covalent association that necessitates the cleavage for the delivery (A), encapsulation inside dendrimers (B), and electrostatic interactions with the terminal. The dendrimers ended by carboxylic acids of type 2-Gn were reacted with an aminolactitol elaborated for being an analog of the amphiphilic galactosylceramide (galb1cer). Galb1cer is present on the surface of cells. It is known that in one of the first events of infection, it acts through its highly specific affinity for the V3 loop region of the gp120 viral envelope protein of HIV-1 [38]. The interaction of the aminolactitol with the dendrimer occurs by proton transfer from the acid of the dendrimer to the amine of the aminolactitol. The idea here was to obtain a chimera of galb1cer, able to interact strongly with gp120, thus inhibiting the action of galb1cer and preventing the infection of cells. Several types of saline dendrimers, built either from the trifunctional core [28] or the hexafunctional core [39] were synthesized, and the same experiments were carried out also with dendrimers ended by various types of phosphonates [30] bearing an alkyl chain of variable length [31]. The influence of the core functionality and number of branches of the dendrimers was clearly identified for the series built from the trifunctional (5a-Gn) and hexafunctional (5b-Gn) cores. Surprisingly, the bioactivity was found core dependent, but not generation dependent [29]. In the case of the phosphonate derivatives (such as 6-Gn), the inhibitory assays indicate that the length of the alkyl chain influences the efficiency of these inhibitors [40].

Challenges and solutions

Despite the benefits of dendrimers as drug delivery carriers, some challenges remain to be solved. The size and surface chemistry of dendrimers are closely related to their toxicity and biodistribution. Size limitation is a primary concern. PAMAM dendrimers of generation 5 or lower can be sufficiently eliminated via glomerular filtration in the renal excretion pathway, while the clearance of PAMAM generation 6 and higher rely more on the hepatic clearance pathway [41]. Dendrimers with sizes ranging from 4–10 nm have the ability to interact with nanometric cellular components and have the capacity to overcome the cellular endocytosis barrier. However, PAMAM dendrimers of generation 6 and higher have high costs and severe toxicity, therefore the higher generation of PAMAM dendrimers are rarely used. Cationic dendrimers possess high binding capacity with nuclei or anion compounds and facilitate cell internalization. However, cationic dendrimers often encounter nonspecific adsorptions of plasma proteins and accelerated elimination by the reticuloendothelial system [42]. In addition, the intracellular dissociation of dendrimers with nuclei acids is limited. Since the interaction of cationic dendrimers with negatively charged cell membranes can result in the destabilization of biological membrane and thus cause cell lysis, cationic dendrimers generally exhibit higher toxicity, especially at high doses, than neutral or anionic dendrimers. Pryor et al. 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 [43]. Recent developments that have been made to address the challenges mentioned above are summarized below. Despite the benefits of dendrimers as drug delivery carriers, some challenges remain to be solved. The size and surface chemistry of dendrimers are closely related to their toxicity and biodistribution. Size limitation is a primary concern. PAMAM dendrimers of generation 5 or lower can be sufficiently eliminated via glomerular filtration in the renal excretion pathway, while the clearance of PAMAM generation 6 and higher rely more on the hepatic clearance pathway. Dendrimers with sizes ranging from 4–10 nm have the ability to interact with nanometric cellular components and have the capacity to overcome the cellular endocytosis barrier. However, PAMAM dendrimers of generation 6 and higher have high costs and severe toxicity, therefore the higher generation of PAMAM dendrimers are rarely used. Cationic dendrimers possess high binding capacity with nuclei or anion compounds and facilitate cell internalization. However, cationic dendrimers often encounter nonspecific adsorptions of plasma proteins and accelerated elimination by the reticuloendothelial system [44]. In addition, the intracellular dissociation of dendrimers with nuclei acids is limited. Since the interaction of cationic dendrimers with negatively charged cell membranes can result in the destabilization of biological membrane and thus cause cell lysis, cationic dendrimers generally exhibit higher toxicity, especially at high doses, than neutral or anionic dendrimers [45]. Pryor et al. 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 [46,47]. Recent developments that have been made to address the challenges mentioned above are summarized below.

CONCLUSIONS

We are drawn to dendrimers because of their distinctive properties, including their interior's sufficient empty volume for drug doping and their multifunctional periphery's capacity to bind to molecules, anchor to surfaces, and interact with chemicals. In order for molecules to be used as biomaterials, they must be biocompatible, which includes being nontoxic, immune-neutral, and biodegradable. Such requirements can be met by dendrimers by selecting the components throughout the synthesis process. In order to create biocompatible dendrimers, dendrons, and dendritic polymers made of dendrons, units of amine branching, amide, and alkyl spacers, or amino acids and sugars, are used. Since these macromolecules have become so easily accessible, researchers have increased the range of fields in which they are used. particularly drug delivery and disease treatment. The literature study included in this review demonstrates that while the majority of dendrimer applications in drug delivery focus on employing dendrimers to improve drug solubility and dissolution, dendrimers have also been employed in cutting-edge methods to enhance the therapeutic action of pharmaceuticals. According to all the activity and interest, dendrimers' use in medication delivery appears to have a promising future. However, the most important factor in determining their potential usage in medicinal products is still how they behave in vivo.

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