International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 14, Issue 2, 2022

Review Article

DENDRIMERS: A REVIEW ON ITS SNYTHESIS, TYPES, PROPERTIES AND APPLICATIONS

JUNMONI NATH*

Department of Pharmaceutics, NEF College of Pharmacy, Saukuchi, lokhra, Guwahati 781040
***Email: junmoninath2014@gmail.com**

Received: 05 Nov 2021, Revised and Accepted: 10 Jan 2022

ABSTRACT

Dendrimers are monodisperse macromolecules with a lot of branches. Dendrimers' structural advantages enable them to play a key role in the field of nano-drug delivery. Dendrimers are ideal for a wide range of biological and industrial applications due to their unique behaviour. The bioactive substances may be readily encapsulated into the inside of the dendrimers or chemically conjugated or physically adsorbed onto the dendrimer surface, tailoring the carrier's desirable features to the active material's unique demands and therapeutic uses. This review summarizes on dendrimer production, characterization, advantages, and potential applications in drug delivery.

Keywords: Dendrimer, Synthesis, Application, Types, Toxicity

DOI: https://dx.doi.org/10.22159/ijcpr.2022v14i2.1964 Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr

INTRODUCTION

Dendrimers are monodisperse, three-dimensional, hyperbranched structures with a central core surrounded by peripheral groups. Their physicochemical and biological qualities are dependent on these factors. Dendrimers typically have three architectural components: a core, branches (an internal layer made of repeated units attached to the core), and terminal groups linked to the branches [1]. The interior chambers created by the dendritic polymer structure allow the medicine to be deposited, enhancing its solubility and stability. These macromolecules are attractive candidates for medicinal excipients because of the aforementioned features. Dendrimers are made up of one atom or a collection of atoms with carbon branches added by a series of chemical processes, resulting in a spherical dendrite structure [2-4].

Dendrimers can behave as drug carriers by encapsulating the drugs inside the dendritic structure or by interacting with drugs via electrostatic or covalent interactions at their terminal functional groups (prodrug) [5]. Drug distribution may be divided into two categories. The first method is *in vivo* breakdown of the drug dendrimer conjugate (covalent bonding of the drug to the dendrimer), which requires the presence of appropriate enzymes or a bond-degrading environment. The second method involves the medication being released as a result of changes in the physical environment, such as pH and temperature. This method is independent of external variables and occurs in the core (endo-receptor) or outer shell (receptor) cavities (exo-receptor) [6, 7].

Synthesis of dendrimers

The two methods used for the synthesis of dendrimers are-

a. Divergent approach: The divergent growth approach was the first to be proposed, and it remains the most used today. This technique is based on Tomalia and Newkome's pioneering work, as well as Vögtle's branching model work [8]. The creation of the dendrimer in the divergent process begins in the core and progresses to the periphery. To enhance the reaction with a new monomer, this approach involves two steps: I coupling of monomers and (ii) activation of the monomer end-group [9]. The divergent growth approach consists of repeating the two preceding processes until the necessary dendrimer production is obtained. The initial generation of the dendrimer begins with the activation or alteration of the core and the coupling of the first monomer, resulting in divergent processing. The first generation (G1) is then deprotected or activated in order to react with additional branched monomers and create the second generation (G2), and so on. When a new layer of branching units is generated, a new generation is created, with the number of branched layers from the core corresponding to the generation number [10]. To avoid deficiently created branches in the divergent method, it is critical that each phase of the reaction be fully finished before adding a new generation [11]. In each stage of the synthesis, the surface of the dendrimer may be readily functionalized and changed, resulting in the desired pharmaceutical excipient at the end. Usually, the divergent approach leads to the synthesis of highly symmetric dendrimer molecules.

b. Convergent Approach: Another way for constructing finely controlled dendritic topologies is the convergent approach. The branching architecture in the convergent method begins from the molecular surface of the dendron and proceeds to a reactive focus point, culminating in the production of a single reactive dendron [12]. Its core operations, like the divergent method, include a coupling phase and an activation step. It allows for more structural control than the prior method. It features a modest number of simultaneous reactions at each development phase, resulting in a product with unrivalled purity and functional diversity. Because of the nanoscale steric problems encountered while connecting the dendrons to the molecular level core, the convergent technique is often confined to the synthesis of just lower generation dendrimers [13].

Types of dendrimers

Dendrimers are classified into the following types:

PAMAM (Poly amido amine) dendrimer

The shape is spheroidal or ellipsoidal [14]. Due to the presence of a lot of functional end groups and empty interior voids, it has a high solubility and reactivity. Eg:-Dendritech TM (USA) [15, 16]

PPI (Polypropylene imine) dendrimer

It has a Di amino butane core structure with primary amines as end groups and as the centre the tertiary propylene amines. These are widely utilised in material science and biology and are available up to G-5. Eg; Asramol by DSM (Netherlands) [17].

Chiral dendrimer

The chirality of the dendrimers was achieved by connecting chiral cores with constitutionally distinct but chemically similar branches. Eg; chiral dendrimers derived from pentaerythritol [18].

Multilingual dendrimers

Dendrimers with numerous copies of a functional group on their surface are known as multicopydendrimers. Eg; VivaGel [19].

Tecto dendrimers

These were composed up of core dendrimers that could be surrounded by additional dendrimers that each performed a specialized job, resulting in a smart therapeutic system that could identify illness and supply API to the known diseased cell. Eg; Stratus® CS Acute Care TM, Starburst®, Mercapto [19].

Hybrid dendrimers

These dendrimers exhibit both dendritic and linear polymer properties. Eg; Hybrid dendritic linear polymer, Polysilsesquioxanes

Amphiphilic dendrimers

These dendrimers have one half which is electron giving, while the other half is electron-withdrawing. Eg; SuperFect, Hydraamphiphiles and bola-amphiphiles [19]

Peptide dendrimers

Peptide dendrimers are peptide dendrimers that contain amino acids in the form of branching or internal units. These are used for both diagnosing and delivering vaccines. Eg; Beta Casomorphin (human) [20].

Frechet-type dendrimers

These were based on a hyperbranchedpolybenzyl ether structure. Dendrimers have a carboxylic acid group linked to their surface, which offers a location for additional functionalization and improves dendrimersolubility. Eg; Frechet type dendronazides, TM Priostar

PAMAMOS (Poly Amidoamine organosilicon) dendrimers

These are commercial dendrimers that include silicon and are inverted unimolecular micelles with outside hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilicpolyamidoamine. Eg; SARSOX [21].

Multiple antigen peptide dendrimers

These are polylysine-based molecular assemblies that look like dendrons. Lysine was a great monomer for the development of numerous branching sites because of its alkyl amino side chain. Eg; vaccine and diagnostic research [21].

Properties of dendrimer

Nanoscale dimensions and shapes

Due to its well-organized synthesis process and size-controllable features, dendrimers have nanoscale dimensions. The diameter of dendrimers with an ethylenediamine core grows from 1.1 to 12.4 nm as they grow from generation 1–10 in the PAMAM dendrimer family. Dendrimer shape can change over time. Low-generation PAMAM dendrimers (G0–G3) with an ethylenediamine core and no internal properties have ellipsoidal forms, but high-generation PAMAM dendrimers (G4–G10) with well-defined cavities have approximately spherical shapes [22-24].

Monodispersity

Dendrimers manufactured step-by-step have well-organized structures with a very low polydispersity (Mw/Mn 1.01–1.05), in contrast to typical linear polymers [25]. It's because of the preparation process's exact synthesis and purification technique. High-performance liquid chromatography (HPLC), size exclusion chromatography (SEC), mass spectrometry (MS), gel electrophoresis, and transmission electron microscopy have all been used to characterise the monodisperse characteristic of dendrimers previously (TEM) [26].

Polyvalency

Polyvalency is advantageous since it allows for variable functionalization; it is also critical in the creation of antiviral therapeutic drugs because it allows for various interactions with biological receptor sites [26].

Solubility and reactivity

Surface functional groups, dendrimer formation, repetitive units, and even the core all influence dendrimer solubility [27]. Dendrimers have been found to be completely soluble in a wide range of solvents. Because of their high solubility in organic solvents, they dissolve quickly and may be characterised in a variety of ways [28]. Furthermore, their high water solubility allows them to be used as solubility enhancers for hydrophobic guest molecules. PAMAM dendrimers, on the other hand, have a high density of surface functional groups (–NH2,–COOH,–OH) that might conjugate with a variety of bioactive compounds. We now have novel nanodevice design methodologies thanks to these surface-modified dendrimers with various functionalities. Dendrimers are a good platform in biological sciences because of their high solubility and reactivity [29].

Dynamic structures

Dendrimer conformation is influenced by both their genesis and the environment in which they dwell. Using Monte Carlo simulations, Welch and Muthukumar discovered that changing the salt content or pH in aqueous solutions might change the shape of dendrimers from dense core to dense shell. As a result, it is hypothesised that dendrimer structures in solutions are extremely dynamic. Higher generation dendrimers, on the other hand, are thought to retain their approximately spherical forms in solutions [30].

Low viscosity

Low viscosity is one of the most essential features of dendritic macromolecules. The viscosity of dendrimers in solutions is much lower than that of linear polymers. Although viscosity increases with the number of monomers, viscosity decreases in dendritic macromolecules beyond a particular generation (typically generation 4). As a result, higher-generation dendrimers have more functional groups and have a lower viscosity than lower-generation dendrimers. This behaviour varies from linear polymers in that the inherent viscosity of these structures grows in lockstep with the molecular mass. The low viscosity is favorable because it simplifies the formation of the dendrimer–drug complex and allows for more rapid drug release [31, 32].

Advantages

1. Direct administration of medication to a patient's afflicted body area.

2. Drugs can also be released in a controlled and continuous manner.

3. Drugs may readily be made to stay inside the layers of skin and not enter the bloodstream.

4. Bypassing the gastrointestinal medium, and so avoiding variations caused by gastric secretions.

5. Reduced clearance of drug owing to changed distribution of the drug in organs at the site of localization and transportation due to regulated and prolonged release of the drug9

6. Drug loading is unusually high.

7. Drug activity is preserved because pharmaceuticals may be integrated into systems without causing a chemical reaction.

8. Other nanoparticles' shortcomings are overcome, such as liposomes' low encapsulation effectiveness, quick leakage of water-soluble drugs in the presence of blood components, and reduced storage stability.

9. Dendrimers are good for targeting solid tumours because of their high permeability and poor drainage in the tumour vasculature, which leads to macromolecule buildup in the tumour (enhanced permeation rate). Targeted delivery (attaching site-specific ligands at the surface or magnetic guiding) also reduces the quantity of medicine used, lowering systemic toxicity [33, 34].

Toxicity of dendrimers

Although there are various benefits to using these nanosystems as a pharmaceutical excipient, it is critical to assess the toxicity of dendrimers. Dendrimers interact with some cellular components, such as the cell membrane, nucleus, and proteins, due to their size (1–100 nm), as these biological constituents have the same dimension span. Furthermore, some metal ions, such as iron and

zinc, may be complexed by dendrimers, altering the biological activity of haemoglobin and renal function, respectively. However, the surface charge of a dendrimer is the most important component in determining its toxicity. Pharmacokinetics and biodistribution have an impact on a polymer's toxicity *in vivo*. As a result, biodistribution experiments are required to determine which tissues or organs have a higher drug storage capacity and, as a result, are possible toxicity targets [35, 36].

Applications

The various applications of dendrimers are:

In targeted gene delivery

Dendrimers can be used as vectors, or carriers, in gene therapy. Genes are transferred into the nucleus by vectors that pass through the cell membrane. Liposomes and genetically modified viruses are currently the most used methods. PAMAM dendrimers have also been used to transport genetic material. Cationic dendrimers (Polypropylenimine (PPI) dendrimer) transport genetic materials into cells by establishing electrostatic complexes with negatively charged genetic materials. Because of their capacity to form compact complexes with DNA, cationic dendrimers provide good non-viral vectors for gene delivery. Another possible use is for the influenza virus to bind to the cell surface using dendrimers coated with sialic acid. Dendrimers are also non-immunogenic, making them ideal as carrier architectures for medicines or bioactive compounds [37].

In pulmonary drug delivery

Because of their huge surface area, thin alveolar region, broad vasculature, and avoidance of first-pass metabolism, the lungs offer an appealing alternate route and location for drug delivery. As a result of this advantage, the drug's systemic bioavailability is improved, resulting in more effective therapeutic action. Many types of dendrimers have been invented, manufactured, and explored for pulmonary administration of different medicines due to their unique structure. These nanosystems have shown to be promising as inhalable drug delivery solutions for the treatment of pulmonary diseases [38]. The PAMAM dendrimer was investigated as a carrier for pulmonary delivery of enoxaparin, low-molecular-weight heparin, to treat vascular thromboembolism by Bai *et al.* [39]. They came to the conclusion that positively charged PAMAM dendrimers are a good nanocarrier for enoxaparin distribution in the lungs without causing injury to the lungs. These researchers also discovered that heparin encapsulated in pegylateddendrimers had a longer circulation half-life and higher pulmonary absorption.

In transdermal drug delivery

Dendrimers with high water solubility and biocompatibility have been demonstrated to increase drug attributes such as solubility and plasma circulation time when used in transdermal formulations, as well as transport pharmaceuticals effectively [40]. For these applications, the viscosity imparting feature of a dendrimer solution enables for easy handling of extremely concentrated dendrimer formulations. Nonsteroidal anti-inflammatory medications (NSAIDs), antiviral, antibacterial, anticancer, and antihypertensive treatments have all been demonstrated to benefit from dendrimers as transdermal drug delivery methods [41]. The model NSAIDs ketoprofen and diflunisal have been explored as transdermal carrier systems using PAMAM dendrimers [42]. The molecular weight of the drug-carrier molecule is known to influence molecular transport through undamaged skin. Because of their large molecular weights, dendrimers failed to improve drug transport through undamaged skin. To further understand the link between dendrimers and skin transport mechanisms, more study is needed in this area.

In ocular drug delivery

For the treatment of numerous ocular illnesses, topical application of APIs to the eye is the most commonly prescribed method of administration. Topically administered medicines, on the other hand, have a very low intraocular bioavailability. This is due to the surplus fluid draining down the nasolacrimal duct and the tears removing the solution. The problems of ocular medication administration can be reduced by adopting specialised delivery methods like dendrimers. Drug delivery methods for the eyes should be sterile, non-irritating, isotonic, biocompatible, biodegradable, and not flow out of the eye. Trivedi *et al.* boosted the bioavailability of pilocarpine in the eye by utilising PAMAM dendrimers containing hydroxyl or carboxylic groups, and the results showed that the drug's resident time was doubled [43].

In enhancing the solubility

PAMAM dendrimers are known to have potential uses in increasing drug delivery system solubility [44]. Dendrimers have hydrophilic exteriors and interiors that are aware of their unimolecular micelle nature and are accountable for their solubilization performance [45]. Dendrimer micelles are unimolecular, and there is no critical micelle concentration. These features make it possible to encapsulate poorly soluble medicines within the dendritic structure and make them soluble. Dendrimer base carriers have the promise of improving the oral bioavailability of difficult-to-absorb medicines [46].

In intravenous drug delivery

The intravenous delivery method is limited in clinical trials due to the poor water solubility of many medicines, particularly anticancer agents. The medications' intravenous administration causes a variety of adverse effects, including hemolysis and phlebitis. Many efforts have been undertaken to produce novel intravenous formulations, with the dendrimer-drug formulation gaining increased interest from developing delivery methods. Before using dendrimers intravenously, their biodistribution throughout the body, as well as their toxicity and immunogenicity, must be evaluated. Meanwhile, the biodistribution of dendrimers *in vivo* following intravenous injection has been thoroughly investigated. Kukowska-Latallo *et al.* studied the biodistribution of tritium-labeled G5 PAMAM dendrimers following intravenous administration and discovered that these materials were rapidly removed from the blood via the kidney on the first day after injection [47].

In site-specific drug delivery

Here the medicine is localised at the desired location. As a result, the medicine does not affect the surrounding tissues. Targeted administration of chemotherapeutics is critical to reducing the major side effects associated with traditional treatment, in which healthy organs such as the liver, spleen, kidneys, and bone marrow can collect dangerous quantities of medication. Surface modification of dendrimers with different targeting moieties such as folic acid (FA), monoclonal antibodies etc may be used to enable region-specific drug delivery [48].

In nasal drug delivery

The trigeminal nerve pathway and the olfactory nerve pathway can both be used to deliver drug molecules to the brain via the nose cavity. By creating a combination with pharmaceuticals, dendrimers have been shown to improve their water solubility. The medicine would be concentrated in the nasal region thanks to this combination. PAMAM dendrimers, for example, have piqued researchers' interest when it comes to nose-to-brain targeting [49]. Perez et al. investigated intranasal delivery using dendrimers by forming dendriplexes (siRNAdendrimer complexes) by attaching radioactive small interfering ribonucleic acid (siRNA) to PAMAM dendrimers and forming these particles into mucoadhesive gels. Dendriplexes also exhibited an increase in radioactivity in the brain [50].

In anticancer drug delivery

Dendrimers' structure and configurable surface activity allow several entities to be encapsulated/conjugated, either in the core or on the surface, making them suitable carriers for anticancer medicines. There are various examples of targeted medication delivery mediated by dendrimers. Jesus *et al.* investigated the use of a 2, 2-bis (hydroxymethyl) propanoic acid-based dendritic scaffold as a doxorubicin delivery carrier *in vitro* and *in vivo* in 2002. *In vitro*, this dendritic nano-formulation with doxorubicin covalently coupled to a high molecular weight three-arm polyethylene oxide by a hydrazone linkage showed decreased cytotoxicity [51]. One of the first instances is PAMAM dendrimerproduction 3.5 coupled to

cisplatin through the sodium carboxylate surface, resulting in a dendrimer–platinate (dendrimer–Pt; 20–25 wt percent platinum) nanoformulation with the capacity to slowly release cisplatin *in vitro* [52]. Lee and colleagues demonstrated that a polyester-based dendrimer–PEO–doxorubicin combination may significantly slow the growth of DOX-insensitive C-26 tumours transplanted subcutaneously in BALB/c mice [53]. For the inclusion of 5FU, Bhadra *et al.* employed PEGylated PAMAM dendrimers [54].

In vaccine delivery

Because most low-molecular-weight compounds are not immunogenic, they must be conjugated to a macromolecule in order to stimulate antibody formation against them. Using dendrimers as nanocarriers of these tiny antigens is now a feasible alternate option for solving this challenge. Dendrimers are ideal immunostimulant chemicals (adjuvants) for improving vaccination efficacy. A number of investigations have been conducted to see if the PAMAM dendrimer is an effective transporter of tiny antigens. The findings showed that following delivery, this nanosystem did not cause any negative host reactions, such as immunological and/or inflammatory responses. PAMAM dendrimers have been effectively employed in antigen conjugates [55].

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Abd-El-Aziz AS, Agatemor C. Emerging opportunities in the biomedical applications of dendrimers. J Inorg Organomet Polym. 2018 Mar;28(2):369-82. doi: 10.1007/s10904-017-0768-5.
2. Noor A, Mahmood W, Afreen A, Uzma S. Dendrimers as novel formulation in nanotechnology-based targeted drug delivery. World J Pharm Pharm Sci. 2015;4:1509-23.
3. Tiwari AK, Gajbhiye V, Sharma R, Jain NK. Carrier mediated protein and peptide stabilization. Drug Deliv. 2010 Nov 1;17(8):605-16. doi: 10.3109/10717544.2010.509359, PMID 20879837.
4. Boas U, Christensen JB, Heegaard PM. Dendrimers in medicine and biotechnology: new molecular tools. Royal Society of Chemistry; 2006.
5. Svenson S, Tomalia DA. Dendrimers in biomedical applications-reflections on the field. Adv Drug Deliv Rev. 2005;57(15):2106-29. doi: 10.1016/j.addr.2005.09.018. PMID 16305813.
6. Patel RP. Dendrimers: A new innovation in drug delivery. Pharm Bio World. 2007;1:42-52.
7. Gillies ER, Frechet JM. Dendrimers and dendritic polymers in drug delivery. Drug Discov Today. 2005 Jan 1;10(1):35-43. doi: 10.1016/S1359-6446(04)03276-3, PMID 15676297.
8. Grayson SM, Frechet JM. Convergent dendrons and dendrimers: from synthesis to applications. Chem Rev. 2001 Dec 12;101(12):3819-68. doi: 10.1021/cr990116h, PMID 11740922.
9. Boas U, Christensen JB, Heegaard PM. Dendrimers in medicine and biotechnology: new molecular tools. Royal Society of Chemistry; 2006.
10. Caminade AM, Turrin CO, Laurent R, Ouali A, Delavaux Nicot B, editors. Dendrimers: towards catalytic, material and biomedical uses. John Wiley & Sons; 2011 Aug 31. p. 1-33.
11. Palmerston Mendes L, Pan J, Torchilin VP. Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. Molecules. 2017 Sep;22(9):1401. doi: 10.3390/molecules22091401, PMID 28832535.
12. Shyma MS, Sheri PS. Dendrimers-a emerging tool for drug delivery. J Pharm Sci Res. 2020 Oct 1;12(10):1309-14.
13. Akbarzadeh A, Khalilov R, Mostafavi E, Annabi N, Abasi E, Kafshdooz T, Herizchi R, Kavetskyy T, Saghfi S, Nasibova A, Davaran S. Role of dendrimers in advanced drug delivery and biomedical applications: a review. Exp Oncol. 2018 Oct 1;40(3):178-83. doi: 10.31768/2312-8852.2018.40(3):178-83, PMID 30285011.
14. Tomalia DA, Naylor AM, Goddard Iii WA. Starburst dendrimers: molecular-level control of size, shape, surface chemistry, topology, and flexibility from atoms to macroscopic matter. Angew Chem Int Ed Engl. 1990 Feb;29(2):138-75. doi: 10.1002/anie.199001381.
15. Esfand R, Tomalia DA. Poly(amidoamine)(PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. Drug Discov Today. 2001 Apr 15;6(8):427-36. doi: 10.1016/s1359-6446(01)01757-3, PMID 11301287.
16. Schiavon O, Pasut G, Moro S, Orsolini P, Guiotto A, Veronese FM. PEG–ara-C conjugates for controlled release. Eur J Med Chem. 2004 Feb 1;39(2):123-33. doi: 10.1016/j.ejmech.2003.10.005, PMID 14987821.
17. Brana MF, Dominguez G, Saez B, Romerdahl C, Robinson S, Barlozzari T. Synthesis and antitumour activity of new dendritic polyamines–(imide–DNA-intercalator) conjugates potent Lck inhibitors. Eur J Med Chem. 2002 Jul 1;37(7):541-51. doi: 10.1016/s0223-5234(02)01362-4, PMID 12126773.
18. Hawker CJ, Wooley KL, Frechet JMJ. Unimolecular micelles and globular amphiphiles: dendritic macromolecules as novel recyclable solubilization agents. J Chem Soc Perkin Trans 1. 1993;12(12):1287-97. doi: 10.1039/P19930001287.
19. Pushkar S, Philip A, Pathak K, Pathak D. Dendrimers: nanotechnology derived novel polymers in drug delivery. Indian J Pharm Educ Res. 2006;40(3):153.
20. Yasukawa T, Ogura Y, Tabata Y, Kimura H, Wiedemann P, Honda Y. Drug delivery systems for vitreoretinal diseases. Prog Retin Eye Res. 2004 May 1;23(3):253-81. doi: 10.1016/j.preteyeres.2004.02.003, PMID 15177203.
21. Tripathy S, Das MK. Dendrimers and their applications as novel drug delivery carriers. J Appl Pharm Sci. 2013 Sep;3(09):142-9.
22. Svenson S, Tomalia DA. Dendrimers in biomedical applications-reflections on the field. Adv Drug Deliv Rev. 2005;57(15):2106-29. doi: 10.1016/j.addr.2005.09.018. PMID 16305813.
23. Esfand R, Tomalia DA. Poly(amidoamine)(PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. Drug Discov Today. 2001 Apr 15;6(8):427-36. doi: 10.1016/s1359-6446(01)01757-3, PMID 11301287.
24. Tomalia DA. Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry. Prog Polym Sci. 2005 Mar 1;30(3-4):294-324. doi: 10.1016/j.progpolymsci.2005.01.007.
25. Guo Z, Pedersen CM, Wang P, Ma M, Zhao Y, Qiao Y, Wang Y. d-glucose Isomerization with PAMAM dendrimers as environmentally friendly catalysts. J Agric Food Chem. 2021 Apr 21;69(17):5105-12. doi: 10.1021/acs.jafc.1c01088, PMID 33881848.
26. Jackson CL, Chanzy HD, Booy FP, Drake BJ, Tomalia DA, Bauer BJ, Amis EJ. Visualization of dendrimer molecules by transmission electron microscopy (TEM): staining methods and cryo-TEM of vitrified solutions. Macromolecules. 1998 Sep 8;31(18):6259-65. doi: 10.1021/ma9806155.
27. Caminade AM, Turrin CO. Dendrimers for drug delivery. J Mater Chem B. 2014;2(26):4055-66. doi: 10.1039/c4tb00171k, PMID 32261736.
28. Frechet JMJ, Hawker CJ, Gitsov I, Leon JW. Dendrimers and hyperbranched polymers: two families of three-dimensional macromolecules with similar but clearly distinct properties. J Macromol Sci A. 1996 Oct 1;33(10):1399-425. doi: 10.1080/10601329608014916.
29. D'Emanuele A, Attwood D. Dendrimer–drug interactions. Adv Drug Deliv Rev. 2005 Dec 14;57(15):2147-62. doi: 10.1016/j.addr.2005.09.012, PMID 16310283.
30. Welch P, Muthukumar M. Tuning the density profile of dendritic polyelectrolytes. Macromolecules. 1998 Aug 25;31(17):5892-7. doi: 10.1021/ma980198w.
31. Inoue K. Functional dendrimers, hyperbranched and star polymers. Prog Polym Sci. 2000 May 1;25(4):453-571. doi: 10.1016/S0079-6700(00)00011-3.
32. Lu Y, An L, Wang ZG. Intrinsic viscosity of polymers: general theory based on a partially permeable sphere model.

Macromolecules. 2013 Jul 23;46(14):5731-40. doi: 10.1021/ma400872s.

33. Dighe NS, Pattan SR, Musmade DS, Gaware VM, Hole MB, Butle SR, Nirmal DA. Chem inform abstract: convergent synthesis: a strategy to synthesize compounds of biological interest. Chem Inform. 2011 Jul 19;42(29). doi: 10.1002/chin.201129232.
34. Mohanraj VJ, Chen Y. Nanoparticles- a review. Trop J Pharm Res. 2006;5(1):561-73. doi: 10.4314/tjpr.v5i1.14634.
35. Maysinger D. Nanoparticles and cells: good companions and doomed partnerships. Org Biomol Chem. 2007;5(15):2335-42. doi: 10.1039/b704275b, PMID 17637950.
36. Duncan R, Izzo L. Dendrimer biocompatibility and toxicity. Adv Drug Deliv Rev. 2005 Dec 14;57(15):2215-37. doi: 10.1016/j.addr.2005.09.019, PMID 16297497.
37. Sideratou Z, Tsiourvas D, Paleos CM. Quaternized poly (propylene imine) dendrimers as novel pH-sensitive controlled-release systems. Langmuir. 2000 Feb 22;16(4):1766-9. doi: 10.1021/la990829v.
38. Mehta P, Kadam S, Pawar A, Bothiraja C. Dendrimers for pulmonary delivery: current perspectives and future challenges. New J Chem. 2019;43(22):8396-409. doi: 10.1039/C9NJ01591D.
39. Caminade AM, Laurent R, Delavaux Nicot B, Majoral JP. 'Janus' dendrimers: syntheses and properties. New J Chem. 2012;36(2):217-26. doi: 10.1039/C1NJ20458K.
40. Cheng Y, Man N, Xu T, Fu R, Wang X, Wang X, Wen L. Transdermal delivery of nonsteroidal anti-inflammatory drugs mediated by polyamidoamine (PAMAM) dendrimers. J Pharm Sci. 2007 Mar 1;96(3):595-602. doi: 10.1002/jps.20745, PMID 17094130.
41. Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta Biochim Pol. 2001 Mar 31;48(1):199-208. doi: 10.18388/abp.2001_5127.
42. Kralj M, Pavelic K. Medicine on a small scale. EMBO Rep. 2003 Nov;4(11):1008-12. doi: 10.1038/sj.embor.7400017, PMID 14593436.
43. Trivedi V, Patel U, Bhimani B, Daslaniya D, Patel G, Vyas B. Dendrimer: polymer of 21st century. J Pharm Int J Pharm Res Bio-Sci. 2012;1:1-21.
44. Vandamme TF, Brobeck L. Poly(amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. J Control Release. 2005;102(1):23-38. doi: 10.1016/j.jconrel.2004.09.015, PMID 15653131.
45. Bai S, Thomas C, Ahsan F. Dendrimers as a carrier for pulmonary delivery of enoxaparin, a low-molecular-weight heparin. J Pharm Sci. 2007 Aug 1;96(8):2090-106. doi: 10.1002/jps.20849, PMID 17286291.
46. Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, Hanifehpour Y, Nejati Koshki K, Pashaei Asl R. Dendrimers: synthesis, applications, and properties. Nanoscale Res Lett. 2014 Dec;9(1):247. doi: 10.1186/1556-276X-9-247, PMID 24994950.
47. Kukowska Latallo JF, Candido KA, Cao Z, Nigavekar SS, Majoros IJ, Thomas TP, Balogh LP, Khan MK, Baker JR. Nanoparticle targeting of anticancer drug improves therapeutic response in animal model of human epithelial cancer. Cancer Res. 2005 Jun 15;65(12):5317-24. doi: 10.1158/0008-5472.CAN-04-3921, PMID 15958579.
48. Kesharwani P, Jain K, Jain NK. Dendrimer as a nanocarrier for drug delivery. Prog Polym Sci. 2014 Feb 1;39(2):268-307. doi: 10.1016/j.progpolymsci.2013.07.005.
49. Parajapati SK, Maurya SD, Das MK, Tilak VK, Verma KK, Dhakar RC. Potential application of dendrimers in drug delivery: A concise review and update. J Drug Delivery Ther. 2016 Mar 14;6(2):71-88. doi: 10.22270/jddt.v6i2.1195.
50. Perez AP, Mundina Weilenmann C, Romero EL, Morilla MJ. Increased brain radioactivity by intranasal P-labeled siRNA dendriplexes within in situ-forming mucoadhesive gels. Int J Nanomedicine. 2012;7:1373-85. doi: 10.2147/IJN.S28261, PMID 22457595.
51. Padilla De Jesus OL, Ihre HR, Gagne L, Frechet JM, Szoka FC. Polyester dendritic systems for drug delivery applications: *in vitro* and *in vivo* evaluation. Bioconjug Chem. 2002 May 15;13(3):453-61. doi: 10.1021/bc010103m, PMID 12009933.
52. Malik N, Evagorou EG, Duncan R. Dendrimer-platinate: a novel approach to cancer chemotherapy. Anticancer Drugs. 1999 Sep 1;10(8):767-76. doi: 10.1097/00001813-199909000-00010, PMID 10573209.
53. Lee CC, Gillies ER, Fox ME, Guillaudeu SJ, Frechet JM, Dy EE, Szoka FC. A single dose of doxorubicin-functionalized bow-tie dendrimer cures mice bearing C-26 colon carcinomas. Proc Natl Acad Sci U S A. 2006 Nov 7;103(45):16649-54. doi: 10.1073/pnas.0607705103, PMID 17075050.
54. Bhadra D, Bhadra S, Jain S, Jain NK. A pegylated dendritic nanoparticulate carrier of fluorouracil. Int J Pharm. 2003 May 12;257(1-2):111-24. doi: 10.1016/s0378-5173(03)00132-7, PMID 12711167.
55. Lee SC, Parthasarathy R, Botwin K, Kunneman D, Rowold E, Lange G, Klover J, Abegg A, Zobel J, Beck T, Miller T, Hood W, Monahan J, McKearn JP, Jansson R, Voliva CF. Biochemical and immunological properties of cytokines conjugated to dendritic polymers. Biomed Microdevices. 2004 Sep;6(3):191-202. doi: 10.1023/B:BMMD.0000042048.18186.ff, PMID 15377828.