IJBPAS, September, 2023, 12(9): 4238-4249

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

AN UPDATED REVIEW ON MODIFICATION OF DENDRIMERS: PROPERTIES, SYNTHESIS, AND APPLICATIONS

DIVYA R, REMYA P.N *, DAMODHARAN N

Department of Pharmaceutics, SRM College of Pharmacy, SRMIST, Kattankulathur, Chennai 603203, Tamilnadu, India

***Corresponding Author: Ms. Remya P.N: E Mail: remyamathavan@gmail.com**

Received 26th July 2022; Revised 19th Sept. 2022; Accepted 11th Jan. 2023; Available online 1st Sept. 2023

https://doi.org/10.31032/IJBPAS/2023/12.9.7419

ABSTRACT:

Dendrimers are modern nano-polymeric globular architectures that are three-dimensional, hyperbranched. They differ from other polymers due to important characteristics such their nanoscopic size, narrow polydispersity index, effective molecular structure regulation, peripheral availability of different functional groups, and internal cavities. Also, in this study we have discussed about the various ways of modification of the Nanoparticles and Dendrimers such as: PEGylated dendrimers as a brain-targeting tool, Medication delivery to the mind by PEGylated dendrimers, etc., as well as other modifications. PEGylation is a technique for optimizing targeted brain delivery. We have also discussed the role of Nano-technology in enhancing physicochemical properties of ETS (Etoposide), Progressed Nano carriers tend to improve solvency/disintegration of the fat-soluble drugs. And in the last section we have discussed about the various kinds of Dendrimers like: Polyether dendrimers, Polypropylene imine (PPI) dendrimers, etc., and the applications of dendrimers in various fields.

Keywords: Dendrimers, PEGylation, Modification, Hyper-branched, Nanoparticles, Target Delivery, Polyether dendrimers, Polypropylene imine (PPI)

INTRODUCTION :

Dendrimers are nano-atom, tree-like expanded designs, which are having radially symmetric particles. Dendrimers are known as single scatter macromolecules, which are having symmetric fanning units around a center. These nano-atoms were first uncovered by Fritz Vogtle in 1978. Arborols are called as a second gathering of the incorporated macromolecules **[1]**. Course atom is

another name of the dendrimer, yet the course term isn't utilized as much as the dendrimer term. Size, shape, and adaptability of the dendrimers changes as the age increments. Thus, the dendrimer atom is known as engineering plan yet not a compound **[2]**. Dendrimers are hyperbranched macromolecules with a painstakingly customized engineering that can be functionalized to change their physicochemical or natural features.

Nano-carriers are broadly acknowledged and acknowledged inferable from their managed drug discharge study just as their restrictive focusing on the system. Predominantly, dendrimers, nanoparticles (NP's) and PEGylated liposomes was utilized for cerebral focusing of drugs, proteins, peptides & hereditary substance, talked about underneath in a word **[3]**. This survey will be useful for researchers and analysts in planning ideal focused on conveyance frameworks for brain-specific conveyance, giving an impressive course time, biocompatibility, and aggregation at the ideal site.

Professor Donald Tomalia discovered Dendrimer, in the year 1985, comprise with a gathering of macro molecules that had unsurprising & exceptionally requested design, they are blended by tedious compound response from a center. The dendrimeric design can be partitioned into 3 principal segments. First - nucleus or center, second - within layers accepted of monotonous atomic units called dendrons, which start age three - the terminal assembly on the surface **[4]**. Dendrimer formed with Greek [- Dendron "tree"] + English [- mer "part"] that insinuate in spreading design of these kind of polymer. These are monodisperse & current Nano meter scales and spherical figure (01-99 nm) **[5]**.

Appraise the ‘poly’ mean amidoamine dendrimer - PAMAM, for example, the synthetic design fills directly in breadth & dramatically in the final gatherings. Therefore, mixes with larger age (G4-G6) present obstructed branches, creating mathematically shut nanostructures, which provide the strengths to transfer drugs **[6]**. Along these lines, molecules which can be bioactive: 1. stacked inner to be conveyed. 2. Which bounce to the layer. The basic structure of Dendrimer is seen in the **Figure 1**.

PROPERTIES OF DENDRIMERS:

A Diversity of Dendrimers exits and each one has different properties like structure, viscosity, non-polar solubility, aqueous solubility, reactivity, synthesis, architecture and shape. The properties of Dendrimers are explained in the **Figure 2**.

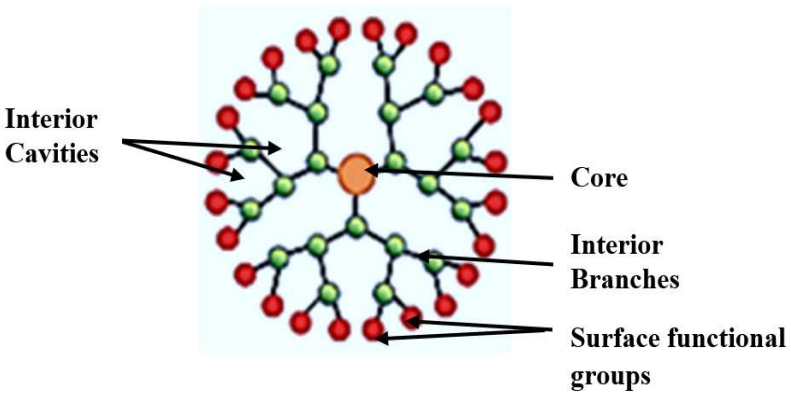

Figure 1: Basic structure of dendrimer

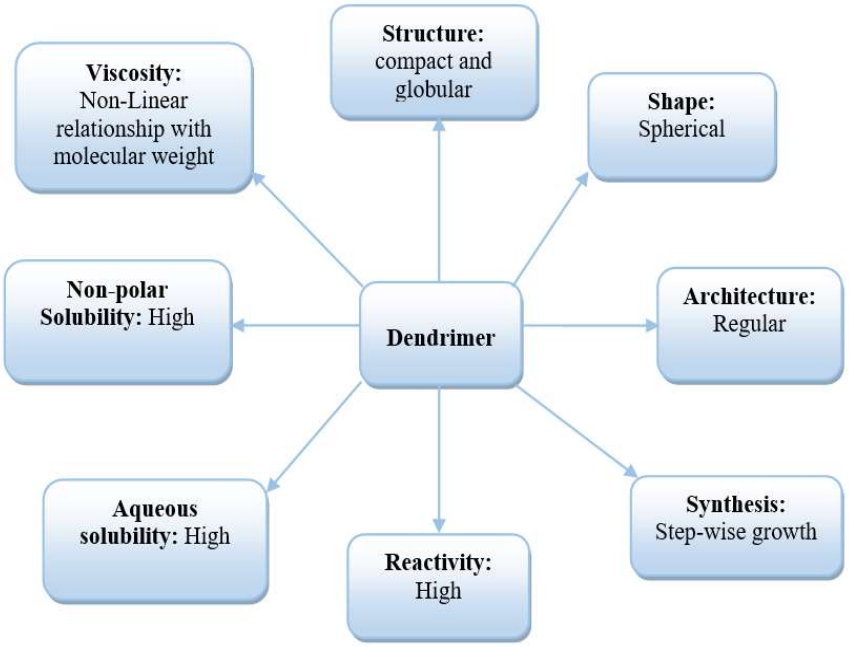

Figure 2: Properties of dendrimers

Advantages [7] [8]

- Dendrimers can be undoubtedly tranquilized.
- They are steady contrasted with liposomes.
- Dendrimers are profoundly water dissolvable because of a lot of terminal utilitarian gatherings and henceforth can be utilized as solubilizer for ineffectively fluid solvent medication molecules.
- Dendrimers likewise draw out the general total percent drug discharge from the platform.

Disadvantages [9] [10]

These molecules have two significant disadvantages: low hydro solvency and high vague poisonousness.

Henceforth, the utilization of dendrimers is a promising procedure.

- Higher expense of creation
- Implementing the manage tests to make sure the dendrimer nature and security**.**

SYNTHESIS OF DENDRIMERS:

Dendrimers can mainly produce by two techniques; one is by molecular chemistry, where the dendritic molecules are organized by the stepwise controlled method. The second one is by polymer method, repetitive branching from the core, which is made of monomers.

1. Synthesis by Divergent method

Divergent methods of synthesis were used in the initial days. The arms are involved to the core in a stepwise manner, like building blocks **[11]**. Divergent method-produced dendrimers are ideal for modifying the end group in the final generation to change the surface molecules, and these dendrimers can also be designed to have specific chemical and physical properties **[12]**.

2. Synthesis by Convergent method

The convergent method of synthesis is opposite to divergent synthesis. First, the dendrons are prepared from the periphery, and then they are joined to the core to form a dendrimer. This synthesis has numerous advantages over the divergent process, but it's complex due to generation's slow process of reaction **[13]**. Usually, Poly (aryl ether) is the skeleton for the dendritic structure, which is synthesized by the convergent method. The divergent and convergent synthesis is given in **Figure 3**.

3. Hyper cores and branched monomer growth in dendrimer synthesis

To obtain better results in this type of synthesis is by the arrangement of oligomer moieties, which are then attached with each other to obtain a dendrimer **[14]**. A core with surface units develops the hyper core, which consists of multiple attaching groups are connected with branched monomer, along with a synthesis of blocks by focal point establishment, which are then linked with a hyper core to synthesize a higher generation of dendrimers.

4. Synthesis of dendrimers by Double exponential growth

These are the linear polymers which consist of fast growth technique. In this synthesis, the starting material is the same monomer for divergent and convergent growth. Then the 2 products interact with each other to give orthogonally secured timer. Repeated growth of timer produces a dendrimer. Due to the rapid growth, divergent and convergent coupling can be done **[15]**.

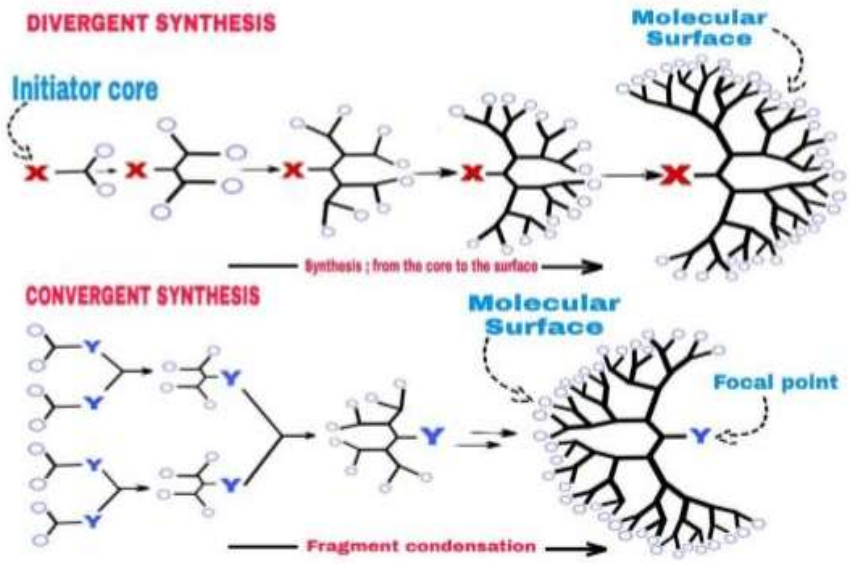

Figure 3: Divergent and Convergent Synthesis of dendrimer

MODIFICATION OF THE NANOPARTICLES AND DENDRIMERS:

PEGylation:

PEGylated NPs explored for drug delivery to the brain

Nanoparticles are particulate dispersions or strong particles varying in dimensions from 10 to 1000 nm. Nanoparticles composed of polymers which are biocompatible as well as biodegradable, like polycyanoacrylate, polycaprolactone, poly (lactic-co-glycolic corrosive), plus chitosan, have been commonly read for concentration on mind **[16]**.

To deliver PEGylated nanocarriers to brain

In general, Nano-carriers are identified and recognized as a consequence of their regulated drug discharge profile, much as they rely selectively on instruments. Basically, PEGylated liposomes, nanoparticles (NPs) and dendrimers were misused, given in detail below for cerebral concentration of hereditary materials, peptides, proteins, and medications. The ways of modification of the Nanoparticles and Dendrimers are shown in **Table 1**.

`PEGylation: a technique for optimizing targeted brain delivery

Polyethylene glycol (PEG) covering or formulation with Nano-carrier structures is referred to as PEGylation. In the area of nanomedicine, PEGylation has become a shelter to provide biocompatibility and to go around nanocarriers opsonin's. PEGylation, however can shield the attention on the ligand and concentrate on the individual cell; however un-PEGylated nanocarriers have rapid release from the

flow of the blood. It decreases the chances pertaining to collaboration or acknowledgment with the perfect receptor site of focused nano carriers and prompts fewer restorative outcomes along these lines **[16]**. The stake is by and large broadly utilized in drug conveyance in view of its few focal points; for example, biodegradability, biocompatibility, hydrophilicity, low characteristic harmfulness, and stealth conduct **[17].** PEGylated focused on Nano-carriers (PEG + focusing on ligand) have indicated better focusing on outcomes when contrasted with PEG or focusing on ligand formation alone. Dendrimers have appeared in this new age like sparkling star in the biomedical domain, spanning from medication delivery to MRI, which involving the growth in chemotherapy as well as vaccinations **[18]**.

Table 1: Ways of modification of the Nanoparticles and Dendrimers [19-21]

S.no	PEGylation methods applied	Utilization
1.	PEGylated dendrimers as a brain-targeting tool:	• Utilized for expanded dissolvability, expanded drug stacking continued and controlled conveyance, the drawn-out living arrangement in the circulation of blood, and expanded tumor take-up. A non-viral quality conveyance vector to the cerebrum. As a channel for the transmission of oligonucleotides and hereditary compounds. Intersection of the BBB just as focusing on the cerebrum. • The transfection fitness of PAMAMPEG-Tf/DNA was discovered as better than PAMAM-PEG/DNA and PAMAM/DNA in BCECs.
2.	Medication delivery to the mind by PEGylated dendrimers.	Conveyance of bioactive into the cerebrum by means of dendrimers to treat different mind sicknesses is an exceptionally encouraging arising field.
3.	Proteins/peptides/Amino acids conjugation:	In many fields, continual exploration employs proteins, peptides, and amino acids as ligands to target a single organ or tissue. With a broad variety of amino acids, peptides and proteins, dendrimers can be produced.
4.	N-acetyl-cysteine (NAC) conjugation:	NAC has been found to be clinically useful in the search for ROS by migrating to intracellular glutathione.

APPLICATIONS:

The various applications of dendrimers are:

1. Dendrimers in biomedical field

Dendritic polymers provide a distinct edge in biomedical applications. Functionally, these dendritic polymers are similar to proteins, enzymes, and viruses. Dendrimers and other molecules can be linked to the periphery or held within dendrimer internal spaces. Polyamidoamine dendrimers, a variant of this substance, are used as potential blood substitutes in modern medicine **[22]**.

2. Dendrimers as imaging agents

Metal chelates based on dendrimers serve as a contrast agent in magnetic resonance imaging. Dendrimers are highly suited and used as image contrast media due to their characteristics. Many studies on dendrimers have showed that they are a more effective contrast agent than traditional ones. Dendrimers have many binding sites on their periphery, which

allows many MRI contrast agent complexes to adhere to them. Depending on production, one dendrimer molecule can store up to 24 distinct agent complexes, resulting in a higher signal-to-noise ratio. Finally, the pharmaceutical sector recognized these dendrimer-based MRI agents, resulting in a variety of commercial advances **[23] [24]**.

3. Dendrimer as Anticancer drugs

The most promising way dendrimers could be used is to deliver drugs in a controlled and specific way, which is also related to the topic of nanomedicine. How to improve the pharmacokinetics of drugs used to treat cancer is one of the most important problems facing modern medicine. Drugs that have been conjugated with polymers have a longer half-life, greater stability, are more water soluble, and are less immunogenic and antigenic. Passive targeting is made possible by the unique pathophysiological traits of tumors, such as excessive angiogenesis leading to hypervascularization, increased permeability of tumor vasculature, and restricted lymphatic drainage. This results in the selective accumulation of macromolecules in tumor tissue. The term "enhanced permeability and retention" refers to this behavior (EPR). The drug-dendrimer conjugates have high solubility, minimal systemic toxicity, and only specific accumulation in solid tumors. Recently, several methods have been developed for encapsulating, complexing, or conjugating dendrimers with pharmaceutical compounds, genetic materials, targeting agents, and dyes **[22]**.

4. Dendrimer in various drug delivery system

A. Oral Drug Delivery

The most commonly utilized route is the oral route. Drug breakdown is caused by stomach acid and enzymes. Because the interior of a dendrimer is hollow, it provides an excellent location for drug entrapment. This trapping improves the drug's solubility and stability.

E.g., PAMAM dendrimers coupled with folic acid and fluorescein isothiocyanate for tumor cell targeting and imaging. Dendrimer provides a protective coating that decreases the influence of acid and enzyme **[25]**.

B. Ocular Drug Delivery

The most commonly prescribed route of administration for the treatment of numerous ocular illnesses is the topical application of active drugs to the eye. Dendrimers offer novel solutions to challenging ocular medication delivery challenges. It is preferable for an ocular drug delivery system to be non-irritating,

biocompatible, sterile, isotonic, and biodegradable.

E.g., Recent challenges in ocular drug administration have been overcome by utilizing PAMAM dendrimers with carboxylic or hydroxyl surface groups to increase the residence period of pilocarpine in the eye. It was hypothesized that these surface modified dendrimers will improve pilocarpine bioavailability **[26]**.

C. Pulmonary Drug Delivery

Dendrimers have been used to transport Enoxaparin to the lungs. Positively charged PAMAM dendrimers of the G2 and G3 generations have been shown to boost the relative bioavailability of Enoxaparin by 40%. After pulmonary delivery, the positively charged dendrimer forms a compound with enoxaparin, which proved useful in treating deep vein thrombosis **[26] [27]**.

D. Transdermal drug delivery

Dendrimers have been used in transdermal medication delivery systems. Drugs are generally hydrophobic in nature, resulting in limited water solubility, which hinders efficient distribution into cells. Dendrimers have been shown to improve medication solubility and plasma circulation time when used in transdermal formulations.

E.g., 1. As penetration enhancers, PAMAM dendrimer complexes with (e.g., Ketoprofen, Diflunisal) have been shown to promote drug permeation through the skin. Ketoprofen and diflunisal demonstrated 3.4 and 3.2times greater permeability when coupled with G5 PAMAM dendrimer, respectively. It has been found that employing indomethacin as the model drug in transdermal drug application improved the bioavailability of PAMAM dendrimers.

2. Flurbiprofen release could be controlled by forming a compound with amine terminated generation 4 (G4) PAMAM Dendrimers **[25] [27]**.

E. Targeted gene delivery

Dendrimers can be used as vectors or carriers in gene therapy. Vectors that pass through the cell membrane deliver genes into the nucleus. Liposomes and genetically modified viruses are currently the most commonly used techniques. PAMAM dendrimers have also been used to transmit genetic material. Cationic dendrimers (Polypropylenimine (PPI) dendrimer) transport genetic materials into cells by establishing electrostatic complexes with negatively charged genetic materials. Cationic dendrimers are ideal non-viral vectors for gene transfer due to their ability to form compact complexes with DNA. Another hypothesis is that the influenza virus will adhere to the cell surface through sialic acid-coated dendrimers. Dendrimers are also non-

immunogenic, making them ideal as drug or bioactive material carriers **[28]**.

5. Dendrimers as Nano-drug

An obvious example is the use of dendrimers as nano-drugs as an antiviral treatment for the herpes simplex virus. As a result of interfering with integrase and/or reverse transcriptase enzyme activity, poly(lysine) dendrimers treated with sulfonated naphthyl groups can reduce virus adsorption early on and virus reproduction later on. As a result, these dendrimers may be able to prevent or minimize HIV transmission as well as other sexually transmitted diseases (STDs). PPI dendrimers with tertiary alkylammonium groups have been demonstrated to have potent antibacterial activity against both Gram-negative and Gram-positive bacteria. Chitosan-dendrimer hybrids have also been proven to be effective antibacterial agents **[25] [27]**.

6. Dendrimer as solubility enhancer

Dendrimer molecules have a hydrophilic exterior and a hydrophilic interior, and they form covalent and non-covalent complexes, resulting in their unimolecular micelle nature. PAMAM dendrimer may improve pharmaceutical solubility. Because dendrimer is a unimolecular micelle, it lacks a critical micelle concentration; as a result of this property, poorly soluble drugs are rendered soluble by encapsulating them within the dendrimer structure. Dendrimer-based nanocarriers improve oral bioavailability in oral drug delivery systems **[27]**.

CONCLUSION:

Dendrimers are used as carriers or scaffolds (drugs, imaging agents, ligands) in the majority of the dendrimer applications reviewed in this study. For targeted delivery of medications to acidic pH locations such as endosomes with a Ph comparable to 5, PEGylated dendrimers can be used. PEGylation has been shown to amplify medication loading, but drug release has been decreased. Dendrimers were jointly modified using a number of techniques to improve siRNA loading, bioavailability, permeability, reduce off target impact, and enhance therapeutic potential in the treatment of diseases like HIV and cancer. Dendrimers are perfect carriers in biomedical applications like drug delivery, gene transfection, and imaging due to their high degree of control over dendrimer design, scale, shape, branching duration and density, and surface characteristics. Bioactive compounds can be encapsulated within the dendrimer, chemically bonded, or externally adsorbed to the dendrimer's surface, with the ability to adjust the carrier's properties to the particular specification of the active substance and its therapeutic applications.

CONFLICT OF INTEREST:

The authors declared no conflicts of interest**.**

ACKNOWLEDGMENTS:

The authors would like to thank SRM College of Pharmacy, SRMIST, Kattankulathur.

REFERENCES:

[1] Campbell, C., Sampathkumar, S. G., Yarema, K.,Campbell, C.T., Sampathkumar, S., Yarema, K.J.2007. Metabolic oligosaccharide engineering: perspectives, applications, and futuredirections. MolecularBioSystems,3:187–194.

[2] Newkome, G.R.1985. Cascade Molecules: A new ApproachtoMicelles.1aA [27]-Arborol. Journal of OrganicChemistry,50(11):2003–2004.

[3] Bosman, A.W., Janssen, H.M., Meijer, E.W. 1999. About Dendrimers: Structure, Physical Properties, and Applications.ChemicalReviews,99(7): 1665–1688.

[4] Tomalia DA, Baker H, Dewald J, Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: starburst-dendritic macromolecules. Polymer journal. 1985 Jan;17(1):117-32.

[5] Kesharwani P, Jain K, Jain NK. Dendrimer as nanocarrier for drug delivery. Progress in Polymer Science. 2014 Feb 1;39(2):268-307.

[6] Esfand R, Tomalia DA. Poly (amidoamine)(PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. Drug discovery today. 2001 Apr 15;6(8):427-36.

[7] Lee CC, MacKay JA, Fréchet JM, Szoka FC. Designing dendrimers for biological applications. Nature biotechnology. 2005 Dec;23(12):1517-26.

[8] Svenson S, Tomalia DA. Dendrimers in biomedical applications—reflections on the field. Advanced drug delivery reviews. 2012 Dec 1;64:102-15.

[9] Gupta U, Agashe HB, Asthana A, Jain NK. Dendrimers: novel polymeric nanoarchitectures for solubility enhancement. Biomacromolecules. 2006 Mar 13;7(3):649-58.

[10] Sanyakamdhorn S, Agudelo D, Bekale L, Tajmir-Riahi HA. Targeted conjugation of breast anticancer drug tamoxifen and its metabolites with synthetic polymers. Colloids and Surfaces B: Biointerfaces. 2016 Sep 1; 145:55-63.

[11] Vogtle F, Buhleier EW, Wehner W. Cascade and nonskid-chain-like syntheses of molecular cavity topologies. Synthesis. 1978; 2:155-8.

[12] Kaminskas LM, Boyd BJ, Porter CJ. Dendrimer pharmacokinetics: the effect of size, structure and surface characteristics on ADME properties. Nanomedicine. 2011 Aug;6(6):1063-84.

[13] Newkome GR, Yao Z, Baker GR, Gupta VK, Russo PS, Saunders MJ. Chemistry of micelles series. Part 2. Cascade molecules. Synthesis and characterization of a benzene [9] 3-arborol. Journal of the American Chemical Society. 1986 Feb;108(4):849-50.

[14] Chabre YM, Roy R. Recent trends in glycodendrimer syntheses and applications. Current Topics in Medicinal Chemistry. 2008 Sep 1;8(14):1237-85.

[15] Kawaguchi T, Walker KL, Wilkins CL, Moore JS. Double exponential dendrimer growth. Journal of the American Chemical Society. 1995 Mar;117(8):2159-65.

[16] Gajbhiye V, Escalante L, Chen G, Laperle A, Zheng Q, Steyer B, Gong S, Saha K. Drug-loaded nanoparticles induce gene expression in human pluripotent stem cell derivatives. Nanoscale. 2014;6(1):521-31.

[17] Tambe P, Kumar P, Paknikar KM, Gajbhiye V. Smart triblock dendritic unimolecular micelles as pioneering nanomaterials: Advancement pertaining to architecture and biomedical applications. Journal of controlled release. 2019 Apr 10;299:64-89.

[18] Huang R, Ke W, Liu Y, Jiang C, Pei Y. The use of lactoferrin as a ligand for targeting the polyamidoamine-based gene delivery system to the brain. Biomaterials. 2008 Jan 1;29(2):238-46.

[19] Yi YS. Folate receptor-targeted diagnostics and therapeutics for inflammatory diseases. Immune Network. 2016 Dec 1;16(6):337-43.

[20] Kelly GS. Clinical applications of N-acetylcysteine. Alternative medicine review: a journal of clinical therapeutic. 1998 Apr 1;3(2):114-27.

[21] Gibson M, editor. Pharmaceutical preformulation and formulation: a practical guide from candidate drug selection to commercial dosage form. CRC Press; 2016 Apr 19.

[22] Abbasi E, Aval SF, Akbarzadeh A, Milani M, Nasrabadi HT, Joo SW, et al. Dendrimers: Synthesis, applications, and properties. Nanoscale Res Lett. 2014;9(1):1–10.

[23] Mathur V, Satrawala Y, Rajput MS. Dendrimers : A Review Dendrimers : A Review. 2015;(February).

[24] Najafi F, Kalajahi MS, Mamaqani

HR, Ethylenediamine EDA. A review on synthesis and applications of dendrimers. J Iran Chem Soc [Internet]. 2021;18(3):503–17. Available from: https://doi.org/10.1007/s13738-020-02053-3

[25] Shahi SR, Kulkarni MS, Karva GS, Giram PS, Gugulkar RR. Review Article:DENDRIMERS. 2015;(July).

[26] Patel HN, Patel PM. Dendrimer applications - A review. Int J Pharma Bio Sci. 2013;4(2):454–63.

[27] Nikzamir M, Hanifehpour Y, Akbarzadeh A, Panahi Y. Applications of Dendrimers in Nanomedicine and Drug Delivery: A Review. J Inorg Organomet Polym Mater [Internet]. 2021;31(6):2246–61. Available from: https://doi.org/10.1007/s10904-021-01925-2

[28] NATH J. Dendrimers: a Review on Its Snythesis, Types, Properties and Applications. Int J Curr Pharm Res. 2022;14(2):21–5.