



VERSATILE APPLICATIONS OF DENDRIMERS IN DRUG DELIVERY SYSTEMS

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ABSTRACT:

Dendrimers are wonder molecules of chemistry possess unique characteristics which have improved the physical and chemical characteristics. Due to the presence of terminal groups they show high solubility, reactivity and miscibility. They possess well defined size, shape, molecular weight and monodispersity which make them a suitable carrier in drug delivery and application. The solubility of poorly soluble drugs is enhanced by the unimolecular nature of dendrimers. Dendrimers for drug delivery have been employed using two approaches (1)*Formulation* (2)*Nano-construct*. Drugs are usually entrapped physically in a dendrimer using non-covalent interactions, but in nano-construct drugs are coupled covalently on dendrimers. The use of PAMAM (Poly amido amine) dendrimers have increased the transdermal permeation and solubility, stability and oral bioavailability of various drugs. Dendrimers are engineered to attach targeting ligands and imaging molecules to create a nanodevice. Dendrimers are referred as modern day polymers which offer good properties than conventional polymers. They are employed for drug delivery, gene therapy, chemotherapy. Dendrimer nanotechnology, due to its multifunctional ability has been emerged as the potential to create next generation nano-devices. This review summarizes exclusively classification, synthesis, mechanism of dendrimers and focuses on versatile applications of dendrimers in drug delivery.

KEY WORDS:

Dendrimer, multifunctional targeting, Nanodevice, PAMAM dendrimers, stability.

INTRODUCTION:

Dendrimers are derived from the “greek” word **Dendros** which means tree like structure and **Meros** means part. They consist of inner core and peripheral shell which are designed as branching architectures with well-defined groups^{1,2}. The 3-dimensional structure of dendrimers gives them unique properties such as nano-scaled, well defined functional groups at periphery, hydrophobic and hydrophilic cavities in the interior and extremely low poly-dispersity. Dendrimers have been applied in biological field due to their high water solubility, biocompatibility, polyvalency, precise molecular weight which have made them an ideal carrier for drug delivery and drug targeting

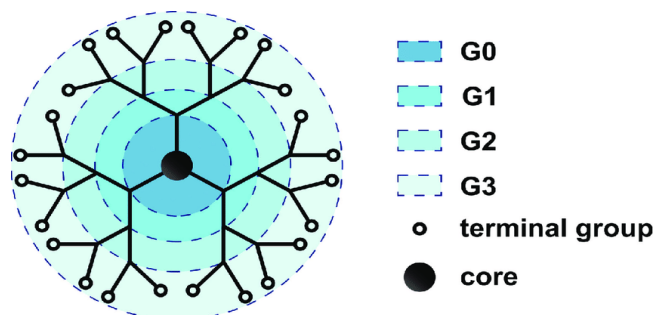


Fig:1 Schematic representation of dendrimer structure³

The dendrimer possess three dimensional structure which gives them a variety of unique properties like nanostructured globular shape, peripheral functional groups, hydrophobic or hydrophilic cavities that are present in the interior and extreme low polydispersity⁴ that are used for wide range of potential applications. Dendrimers have globular structures which contain molecular diameter less than 10 nm, that can be modulated by changing different dendrimer generations. Due to this property the dendrimers possess similar sizes and shapes as specific proteins and biomolecules which make them perfect as biomimics⁵. Also, the highly regular branching of dendrimer pattern permeate the architecture of dendrimers with maximum number of functional groups that are peripherally located⁶⁻⁹. The hydrophobic and the interior hydrophilic cavity of dendrimers make them more useful candidates as unimolecular micelles for the encapsulation of drug molecules¹⁰⁻¹². Since the dendrimers possess low polydispersity the biodistribution of prodrugs that include polymeric drugs can be used as scaffolds¹³⁻¹⁴.

During the last decade, dendrimers have proved to be nanocarriers for different drugs which include anti-inflammatory, antimicrobial, and anticancer drugs that are administered in different routes of drug administration¹⁵⁻¹⁶. However, the application of dendrimers as scaffolds of prodrugs is particularly interesting¹⁷. Dendrimers are included in the drug discovery by their activity against diseases such as inflammation, HIV, herpes simplex virus (HSV), Alzheimer's disease bacteria, and cancer¹⁸. The folded proteins generally produce densely packed interiors and surfaces that usually possess high heterogeneous domains of functionality, hydrophobicity and hydrophilicity. Dendrimers are usually robust, covalently fixed, three-dimensional structures which possess both an interior core which contain solvent (nanoscale container) and an exterior core which is homogenous, mathematically defined as PAMAM dendrimers. Proteins are amphiphilic molecules that use macromolecular scaffolds to regulate the presentation of functional groups at their surfaces. Recently, polymeric scaffolds are made to achieve biomimetic functions. The participation of binding to heparin or HSPG results in potential targets for antiangiogenic activity.

CLASSIFICATION OF DENDRIMERS:

1. PAMAM (Poly Amido Amine) Dendrimer:

These are Synthesised by Divergent method-They are spheroidal or ellipsoidal in shape¹⁹. They have high solubility and reactivity due to large number of functional end groups and internal cavities.

2. PPI (Poly Propylene Imine) Dendrimer :Divergent method- The core contains Di amino butane with primary amines and tertiary propylene amines are present at the centre. These are commercially available up to G-5 and are extensively used in material science and biology

3. Chiral Dendrimer:Convergent method- Chiral dendrimers are derived from pentaerythritol

4. Multilingual Dendrimers: Convergent method –They contain several copies of functional groups on their surface

5. TectoDendrimers:Divergent method-These were made up of core dendrimers, which can be surrounded by other dendrimers.

- 6. Hybrid Dendrimers:** Divergent method- These dendrimers have characteristic of both dendritic and linear polymer.
- 7. Amphiphilic Dendrimers:** Divergent method- These have one half that is electron donating and another half is electron retreating.
- 8. Peptide Dendrimers:** Convergent method- Peptide dendrimers contain an interior unit such as amino acid amino as a branching unit. These are used for the diagnostic purpose and vaccine delivery²⁰.
- 9. Frechet-Type Dendrimers:** By Convergent method. Carboxylic acid group provide functionalization and also improve the solubility of dendrimers which is attached on the surface of the dendrimers.
- 10. Multiple Antigen Peptide Dendrimers:** Convergent method- These are dendron-like molecular assembly based upon a polylysine frame. Lysine contain alkyl amino side-chain which is a monomer of frequent branching points.

Molecular structure, dendrimer generations and its components:

Dendrimers are built from atoms such as nitrogen to which elements such as carbon are added by repetitive chemical reactions which produce a spherical branching structure. Final shape is spherical macromolecular structure which is similar to blood albumin and haemoglobin in size. Dendrimers generation are hyperbranching when going from centre of the dendrimer to the periphery. The core structure do not contain focal points as the hydrogen substituents are not considered focal points. Outer shell is space between surface and branching point. Dendrimer interiors are referred as inner shells. In PAMAM and PPI dendrimers pincers are half the number of surface groups since these dendrimers divide into two dendrimers at focal points. Terminal group or surface group is generally referred as end group of the dendrimer.

Physicochemical characterization of dendrimers:

Various analytical techniques are reported in literature to research the physicochemical parameters of dendrimers. Several methods used are spectroscopic, dynamic light scattering (DLS), microscopic, chromatographic and mass spectroscopy; small angle X-ray scattering, small angle neutron scattering, laser light scattering; atomic force microscopy (AFM), transmission microscopy (TEM); size exclusion chromatography, high performance liquid chromatography (HPLC); DSC, temperature modulated calorimetry and dielectric spectroscopy; Polyacrylamide gel electrophoresis (PAGE) and capillary electrophoresis of these dendrimer characterization techniques cannot be used to study the dendrimer-drug conjugates/complexes. Chemical shifts of methylene protons of the G2 dendrimers were determined by NMR spectroscopy which apparently was changed with the addition of silybin. The downfield chemical shift within the outermost layer of the G2 dendrimer and therefore the interior methylene protons confirmed the electrostatic interactions between the amine functional groups of the dendrimer and the phenolic hydroxyl groups. HPLC method was used to determine the solubility of silybin and plasma drug concentration of silybin. The studies indicated that spherical micelles got transformed to worm-like micelles of the BE copolymer as a results of encapsulation of paclitaxel molecules²¹. The formed complexes were investigated for 3 variables.

Factors Affecting Dendrimer Properties:

Effect of pH:

The structural behaviour of PAMAM dendrimers on application of molecular dynamics showed that the dendrimer has an extended conformation, that supported a high ordered structure at a really low pH (pH10). The contraction of the dendrimer takes place because the charge of the molecule becomes neutral and acquiring a more spherical (globular) structure, where the repulsive forces present between the dendrimer arms and the surface groups reaches a minimum value. At this particular pH, the conformation features results as a higher degree of back-folding, as a consequence of the weak "inter-dendron" repulsive forces.

Effect of Solvent :

The solvation power of any solvent to solvate the dendrimer may be a vital parameter when investigating the conformational state of a dendrimer. Dendrimers generally exhibit a greater extent of back-folding with decreased solvent quality, i.e. decreasing solvation. The low generation dendrimers shows the very best tendency towards back-folding to poor solvation in comparison to the upper generation dendrimers. Weak acidic solvent like chloroform act as hydrogen donor for the inside amines during a basic dendrimer

like PPI, resulting in an extended conformation of the dendrimer due to hydrogen bonding between the solvent and therefore the dendrimer amines.

Effect of Salt:

High ionic strength (high concentration of salts) effect charged PPI dendrimer with a high degree of back-folding which is analogous to what is observed by increasing pH or poor solvation. At low salt conditions, the repulsive forces between the charged dendrimer segments leads to an extended conformation so as to attenuate charge repulsion within the structure resulting in a decreased surface polarity of the back-folded dendrimer.

Effect of Concentration:

In dendrimers with flexible structures the conformation is not only suffering from small molecules like solvents, salts or protons but can also be sensitive to larger objects, like other dendrimers or surfaces that affect molecular density and dendrimer conformations. Small angle X-ray scattering (SAXS) experiments that's performed on PPI dendrimers (G4, G5) using polar solvent like methanol showed that molecular conformation of dendrimers gets increased because the concentration becomes increased.

Synthesis of Dendrimers:

Dendrimers are in between molecular chemistry and polymer chemistry. They are a neighbourhood of molecular chemistry due to their step-by-step controlled synthesis, and that they are mentioned as polymers due to their repetitive structure which is formed of monomers²³⁻²⁵. The macromolecular classes (i.e., linear, cross-linked, and branched) are made to get rather polydisperse products of different molecular weights. The synthesis of dendrimers provide the prospect of generating monodisperse, structure-controlled macromolecular structures which are almost like those like in biological systems²⁶. They are prepared by divergent method or convergent method²⁷. In another method, the dendrimer grows outward from a multifunctional core molecule. The core molecule reacts with the monomer molecules containing one active and two inactive groups, giving the first-generation dendrimer. For reactions with more number of monomers the new periphery of the molecules gets activated. The classical polymerization process which ends up in linear polymers is typically random in nature and produces molecules of various size, whereas size and molecular mass of dendrimers are often specifically controlled during synthesis. 1. Divergent Method 2. Convergent Method 3. Double Exponential and Mixed Method 4. Hypercores and Branched Monomers Growth.

Divergent Method Characteristics:

Dendrimer formation start from core.

Merit:-Large quantity of dendrimer produced by this method.

Demerit:-To prevent the problem during synthesis great quantity of reagent is required. Product purification is extremely tedious.

Convergent Method Characteristics:

Dendrimer formation from Surface.

Merit:-Defects within the final structure are less. Product easily purified.

Demerit:-Due to steric hinderance higher generation dendrimer cannot be formed It is a tedious task.

Double exponential and mixed method:

Characteristics:-In this method both Divergent and Convergent methods are used.

Merit: Higher yield with fewer steps.

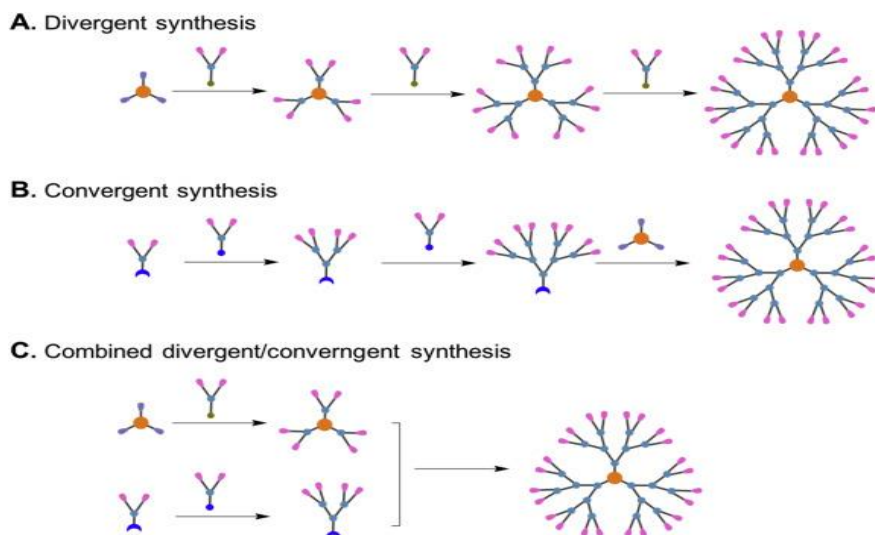


Fig 2: Synthesis of Dendrimers ²⁸

Hypercores and branched monomers growth:

Characteristics :This method involves the pre-assembly of oligomeric species which may be linked together to offer dendrimers.

Merit :Fewer steps, Higher yields.

Demerit: Rapid climb technique for linear polymers, Fast method.

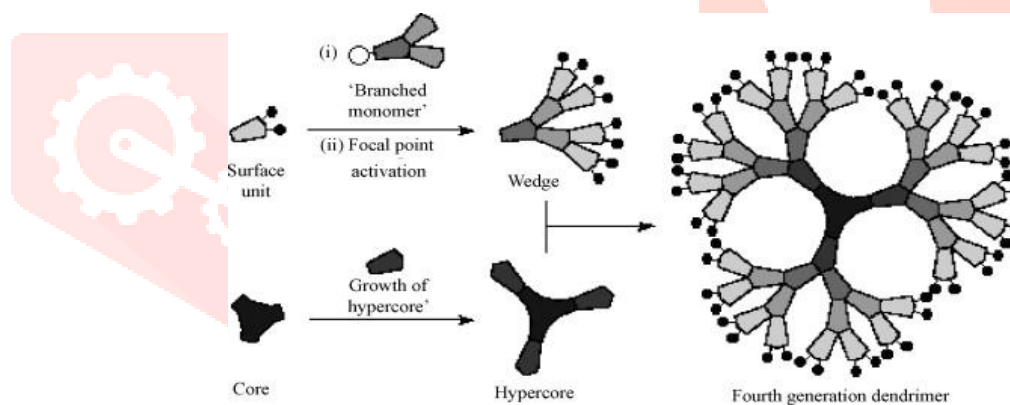


Fig 3: Hypercores and branched monomer growth ²⁹

Factors Affecting Dendrimer Synthesis:

There are various factors which affect dendrimer synthesis are following:

- Incomplete chemical reaction
- Intermolecular cyclization
- Fragmentation
- Solvolysis of terminal functionalities.

ADVANTAGES OF DENDRIMERS:

- * Controlled drug release
- * Improved bio-availability

- * Better patient compliance
- * Increased solubility, stability, permeability of medicine
- * Improved delivery efficiency
- * Viral diagnosis
- * Increased half-life
- * High uniformity and purity
- * Reduced side effects
- * Rapid cellular entry

Mechanism of Drug Delivery Through Dendrimers:

Dendrimers offer a high drug-loading capacity and that they are attractive in nature. The 3D structure and functional groups of dendrimer surface can load drug molecules to the inside of the dendrimers and attached to the surface groups. Encapsulation of medicine and dendrimer-drug conjugates are the 2 main methods of drug delivery³⁰⁻³¹.

1. Non-covalent Encapsulation of drugs/Host-Guest Relaxation:

The non-bonding interactions with specific groups within dendrimer (Physical Entrapment) end in incorporation of small organic molecules. Encapsulation of drug uses bulk of exterior of dendrimer and interactions between dendrimer and drug to trap the drug inside the dendrimer. Dendrimers are often used as dendritic boxes and unicellular micelles for the incorporation of hydrophobic/hydrophilic molecules. The dendritic unicellular micelles contain the hydrophobic cores which are surrounded by hydrophilic shells over polymeric micelles. Such micellar structure is maintained in the least concentrations.

2. Covalent dendrimer drug conjugates:

The dendrimer which is attached to drug molecule end in complex formation. The resultant complexes are formed due to electrostatic interactions between drug and dendrimer or conjugation of drug to dendrimer molecule. Through these interactions various ionizable drugs form complexes with ionizable terminal surface groups of dendrimers. In dendrimer-drug conjugates, drug is attached through chemical bond on to the surface groups of dendrimer. With the assistance of spacers the drugs are often covalently conjugated to the dendrimers. Spacers include PEG, p-amino carboxylic acid, lauryl chains, hippuric acid, biodegradable ester bond.

Dendrimer Drug Delivery Strategy:

The PAMAM dendrimers are one among the foremost used dendrimers for drug delivery systems. The dendrimer has 3 main sites for drug entrapment using several mechanisms.

1. Void spaces (molecular entrapment)
2. Branching points (hydrogen bonding)
3. Outside surface groups (charge-charge interactions)

Drug entrapment depends on structure of dendrimer and drug, so selection of appropriate dendrimer is the main step for drug entrapment. Right combinations of dendrimers are achieved by screening one dendrimer with the another one. PAMAM dendrimers are commercially available with amine, hydroxyl, carboxylate and pyrrolidine groups.

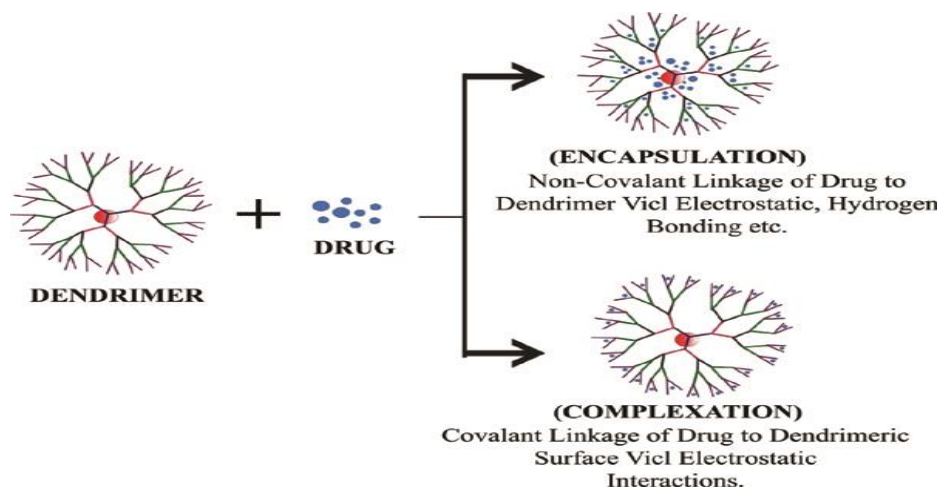


Fig 4: Encapsulation and Complexation ³²

Multifunctional Delivery System:

Dendrimers provide several works like drug solubility and targeting of the drug. They can be used as multifunctional excipients. PAMAM dendrimers are water soluble molecules and their ability to entrap hydrophobic molecules make them good enhancers of solubility. With increase in dendrimer generations, drug entrapment can be increased which is size dependent. On solubilization of hydrophobic molecule, the dendrimer drug complex often enhances drug dissolution, stability, bioavailability.

APPLICATION OF DENDRIMERS IN DRUG DELIVERY:



Fig 5: Applications ³³

1. Dendrimers in CNS Drug Delivery:

The occurrence of degenerative diseases in brain will simultaneously increase the aging population. The blood-brain-barrier (BBB) within the brain acts as a best gatekeeper in the body for exogenous substances. The BBB is crucial for maintaining the health of the brain because it hinders the efforts for delivery of therapeutic agents to the brain. The poor permeable nature of some drugs is especially thanks to the tight junctions of the BBB and efflux transporters. Due to the ineffectiveness of conventional drug therapies, NANOMEDICINE has shown an excellent effect for treatment of the many CNS diseases. Nano carriers are prepared by the biomedical and pharmaceutical application of nanotechnology. Among these dendrimers are paid great efforts due to its major advantages like:

- High uniformity and purity
- Low toxicity and immunogenicity
- Rapid cellular entry

- Improved delivery efficiency

2.Dendrimers In Oral Delivery:

The drug delivery through the oral route is taken into account the simplest means of drug administration. Dendrimers are effective in oral drug delivery because dendrimers loosen the tight junctions of epithelial layer and improve absorption of small relative molecular mass drugs. Dendrimer–ibuprofen conjugate improve the efficacy of drug by enhancing cellular delivery and rapid pharmacological effects are produced.

3.Dendrimers In Nasal Delivery:

Development of non-invasive and safer alternative drug administration to i.v.administration is very preferred due to their poor patient compliance .Transmucosal routes just like the mucosal linings of the nasal, rectal, vagina, ocular and mouth provide many advantages for systemic drug delivery. Nasal administration provides an alternate for achieving systemic drug effects to the parenteral route, which can be inconvenient for oral administration and end in low bioavailability. The dendrimers with charge cause increased transport of medicine to the brain as positively charged particle show an increased association of mucus and greater cellular uptake.

4.Dendrimers In Gene Delivery:

The ability to transfer genetic material efficiently, into the nucleus and cytoplasm of eukaryotic cells allow treatment of a spread of genetic disorders. Commonly two approaches are used.Viral and nonviral based gene delivery to focus on cells.The viral carriers (Synthetic DNA delivery systems) can show rapid transfection,low efficiency, immunologic and oncologic adverse effects that are related to these vectors.Nonviral gene delivery vectors allow the usage of natural/synthetic molecules or physical forces to transfer genetic material to targeted cells.Dendrimers are one among the foremost useful non-viral gene delivery systems which play a big role within the development of non-viral vectors for gene delivery,due to their ability to transfect cells without inducing toxicity, the high density charge and functional surface groups which permit formation of nanostructures with DNA, the so called “dendriplexes”(8,9) and optimal condensation.PAMAM dendrimers are used as a possible nonviral gene delivery agents to their cationic nature which enables deoxyribonucleic acid (DNA) binding at physiological pH.6.(10).

5.Dendrimers In Vaccine Delivery:

Most of the low relative molecular mass substances are not immunogenic, they need to be conjugated to a macromolecule. The unmodified PAMAM dendrimers which fail to elicit an antibody response on their own become haptenized upon protein conjugation and can generate a dendrimer-mediated antigenic response. These molecules are ideal carriers of small antigens that make it possible to organize multimeric antigenic conjugates(11,12) with well-defined molecular properties for human use.

6.Dendrimers in Administration of Drug:

The appliance of dendrimers in pharmaceutical and medical chemistry is fast and becoming one of the foremost attractive areas of dendrimer chemistry and thus the potential of dendrimers as drug administration agents has been explored for several researchers.Conjugation of propranolol to lauroyl-G3dendrimers further increased its A→B Papp. Furthermore, they show that the A→B Papp of propranolol conjugates was reduced within the presence of the endocytosis inhibitor colchicine, suggesting that the enhancement mechanism involves endocytosis-mediated transepithelial transport . The A→B Papp of conjugated propranolol wasn't altered within the presence of the P-gp inhibitor cyclosporine. Conjugation of drug to dendrimer allows efflux transporter to bypass it.

7.Dendrimers in Cell Repair:

Intact extracellular matrices(ECMs) have demonstrated potential as biomaterials in various tissue engineering and clinical applications [15,16].These ECM scaffolds provide a natural three-dimensional support to assist the initial mechanical requirements necessaryto support damaged or excised tissue . ECM provides cellular recognition which is important for initial cellular attachment, subsequent cellular differentiation, in-growth of vascular networks, and secretion of latest ECM requisite for eventual scaffold remodeling and tissue regeneration. Dendrimer works as a linker to the scaffold and as a carrier of bioactive molecules. Conveniently during this way, scaffold stability also can be tailored by controlling the extent of cross-linking, which has the advantage of extending their in vivo life.

8. Dendrimers in Vaccine Development:

Vaccination has proven to be a very cost-effective way of controlling infectious diseases caused by microbial pathogens and has been known in its modern form since the pioneering age of the late 18th century. When Jenner introduced vaccinia (cowpox virus) as the primary reliable vaccine [27]. Subsequently, many other successful vaccines are developed, empirically, on the basis of attenuated or killed microorganisms or their toxins. Nevertheless, efficient vaccines are still needed for HIV-1, tuberculosis, malaria, and a spread of respiratory and intestinal infectious diseases. Vaccination has been a robust tool for eradicating smallpox and decreasing formerly widespread diseases like polio, measles, and rinderpest. Even so, a wide range of infectious diseases are still abundantly present around the world (malaria, tuberculosis, and bacterial and viral diarrhoea being the foremost widespread). Such diseases are generally caused by complex pathogens where more rational approach in vaccine design is required. [24]

9. Dendrimers In Topical And Transdermal Drug Delivery:

The transdermal drug delivery offers a safe administration of therapeutic agents. They provide constant drug concentration and avoid peaks and valleys in the peak-plasma concentration. The pain can be reduced as in case of traditional drug delivery as the therapeutic agents will simplify the dosing schedule. Improved patient compliance is seen in TDDS in which drug delivery by transdermal route is limited because of slower rate due to the dense layers formed by the epithelial differentiation and cornification (14). The drug penetration through the skin can be enhanced with the help of penetration enhancers. Polymeric enhancers containing both hydrophilic and hydrophobic portions have been employed. PAMAM dendrimers increase the water solubility and stability of hydrophobic drugs. Dendrimers have potential effects like controlled release and improved drug solubilization.

10. Dendrimers In Pulmonary Drug Delivery:

The drug delivery through lungs is a non-invasive systemic delivery by increasing the surface area for local drug action and systemic drug absorption. The first pass metabolism is avoided and drug is directly to the site of action. The advantages of nanocarrier based drug delivery systems like dendrimers are:

- Enhanced drug solubility
- Delivery of macro molecules
- Reduced side effects
- Reduced dosing frequency
- Improved patient compliance

11. Dendrimers As Solubility Enhancer:

Recent technologies have shown an impact for drug delivery that enhance the bioavailability of drugs. The size, branching density of dendrimers enhances solubility of poorly water soluble drugs. Drugs containing smaller molecules like anti-cancer, anti-inflammatory and anti-microbial drugs have been formulated with PAMAM hydrophilic dendrimers. Dendrimers are unimolecular in nature and contain hydrophilic exteriors and interiors and form non-covalent complexes with drug molecules which enhance solubility (15).

12. DENDRIMERS IN CELLULAR DELIVERY:

The main objective is to deliver the therapeutic drug or gene to a specific intracellular site for desired local action. Surface functionalized (31) dendrimers they can enter the cells to deliver the therapeutic agent. The intracellular dendrimer delivery involves extracellular drug delivery at interstitium and intracellular delivery on internalization. The function of the carrier is to mask all unwanted interactions between the drug and the environment until drug is released from carrier at the target site.

13. Dendrimers In Intravenous Drug Delivery:

The simplest way for delivering a drug into the systemic circulation (26) involves intravenous delivery. Dendrimer drug delivery formulations is emerging as an attractive route for reducing side effects of drugs like anti-cancer drugs.

Table 1.Applications of Pamam Dendrimers

S.No	Drug	Result	Reference
1	Penicillin V, Gadollenium Methotrexate, NH ₂ (G0-G4)	Enhance the solubility and controlled release	34
2	Cisplatin	Slow release, low toxicity	35
3	5-Amino Salicylic acid	Enhance solubility,	36
4	Benzoic acid	Increased solubility	37
5	Indomethacin	Release kinetics	38
6	Propranolol	Controlled drug release	39
7	Venlafaxine	Enhance solubility	40
8	Piroxicam	Controlled drug release	41
9	Diflunisal	Improvement of drug permeation through skin	42

Table 2.Applications of G Pamam Dendrimers:

S. No	Type	Drug	Result	Reference
1	G1 Pamam	PhiPhilux	Delivery of drug with cell killing efficiency	43
2	G2 Pamam and G4 Pamam	Pilocarpine	Prolonged corneal residence time	44
3	G3 Pamam	AIPcS4	Effective drug release to target tissue	45
4	G3 Pamam	Paclitaxel	Increase the solubility	46
5	G3 Pamam	5- Amino levulinic acid	Enhanced photodynamic effect	47
6	G3 Pamam	Timolol maleate	Improved solubility	48
7	G3 Pamam	Sulfamethoxazole	Increased antibacterial activity	49
8	G4 Pamam	Furosemide	Increase the solubility	49
9	G5 Pamam	Cetuximab	Tumor targeted drug delivery	50
10	G5 Pamam	Nifedipine	Enhanced solubility	51
11	G6 Pamam	RGD 8	Enhanced gene	52

Table 3.Miscellaneous Dendrimers:

S.no	Type	Drug	Result	Reference
1	PEG dendrimers	Epirubicin	Increased blood residence time	53
2	PEG dendrimers	Epirubicin prodrug	Improved therapeutic action	34
3	PPI dendrimers	Doxorubicin	Higher cell uptake reduce toxicity	46
4	PPI dendrimers	Etoposide	Increase solubility and in vitro drug release	54
5	PPI dendrimers	Efiveranz	Targetted delivery	55
6	Pamam- PEI-g-PEG	Zidovudine	Effective cellular uptake increase target selectivity	56
7	Carboxylated poly (Glycerol succinic acid)	10-Hydroxycampotheicin	High cytotoxicity	57
8	Manosyllated PPI	Rifampicin	Sustain release and targeted delivery	58

Recent Advances and Future Prospects:

- 1.HIV infected macrophages are targeted in vitro by using dendrimers
- 2.Plasmid and Doxorubicin co delivery targeting to tumour

A future pharmaceutical products containing dendrimers are available within the market. It holds great potential adding value to the pharmaceutical products.

- a. Reducing cost of dendrimer synthesis to be applied in membranes and other fields.
- b. Enlarging membrane applications from hyper branched polymers to field of resource and environment.
- c. New applications of dendritic polymers in other fields of membrane have been exploited.

Conclusion:

Dendrimers are a superb drug delivery systems and holds a promising future in various fields like pharmaceutical, therapeutic, and diagnostic thanks to characteristics like condensed structure, ability to acknowledge specific tissue, versatility, multivalency, high branching degree. By the tactic of surface engineering, dendrimers cytotoxicity of dendrimers are often reduced. Significant advances and innovations have resulted during a wide selection of dendritic architecture and delivery methodologies that promise to become an integral part of medicine in future. As research progresses, newer applications of dendrimers will emerge and future is predicated on dendrimer based drug delivery system.

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REFERENCES:

1. Boas U, Jørn Bolstad Christensen, Heegaard PMH, "Dendrimers in medicine and biotechnology: new molecular tools", 2006, 62-70
2. Jansen JF, de Brabander- van den Berg EM, Meijer EW. Encapsulation of guest molecules into a dendritic box. *Science* 1994; 266:1226-9.
3. Dariusz T. Mlynarczyk, Tomasz Kocki, et al, Dendrimer structure diversity and tailorability as a way to fight infectious diseases. *Intech* 2017.
4. Jain NK, Gupta U, Application of dendrimer-drug complexation in the enhancement of drug solubility and bioavailability, *Expert Opin Drug Metab Toxicol*, 2008; 2003:1035-1045.
5. Chauhan AS, Jain NK, Diwan PV, Khopade AJ. Solubility enhancement of indomethacin with poly(amidoamine) dendrimers and targeting to inflammation. 2004.
6. Barbara K and Maria B. Dendrimers: properties and application. *Acta Biochimica Polonica*, 2001; 48 (1): 199-208. ory regions of arthritic rats. *J Drug Target* 12:575-583.
7. Bai S, Thomas C and Ahsan F. Dendrimers as a carrier for pulmonary delivery of enoxaparin, a low molecular weight heparin. *J Pharm Sci*, 2007; 96 (8): 2090 - 106.
8. Chai M, Niu Y, Youngs WJ and Rinaldi PL. Structure and conformation of DAB dendrimers in solution via multidimensional NMR techniques. *J Am Chem Soc*, 2001; 123: 4670-8.
9. Chauhan AS, Jain NK. Dendrimer mediated transdermal delivery; enhanced bioavailability of Indomethacin. *J. Controlled Release* 2003; 96:537-540.
10. Sonke S and Tomalia DA. Dendrimers in biomedical applications reflections on the Field. *Advanced Drug Delivery Reviews*, 2005; 57: 2106 - 29.
11. N. A. Peppas, "Star polymers and dendrimers: prospects of their use in drug delivery and pharmaceutical applications," *Controlled Release Society Newsletter*, vol. 12, pp. 12-13, 1995.

12. R. Esfand and D. A. Tomalia, "Poly(amidoamine) (PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications," *Drug Discovery Today*, vol. 6, no. 8, pp. 427–436, 2001.
13. D. A. Tomalia, "Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry," *Progress in Polymer Science*, vol. 30, no. 3-4, pp. 294–324, 2005.
14. B. Klajnert, M. Cortijo-Arellano, J. Cladera, and M. Bryszewska, "Influence of dendrimer's structure on its activity against amyloid fibril formation," *Biochemical and Biophysical Research Communications*, vol. 345, no. 1, pp. 21–28, 2006.
15. J. B. Wolinsky and M. W. Grinstaff, "Therapeutic and diagnostic applications of dendrimers for cancer treatment," *Advanced Drug Delivery Reviews*, vol. 60, no. 9, pp. 1037–1055, 2008.
16. Aulenta F, Hayes W, and Rannard S, "Dendrimers: a new class of nanoscopic containers and delivery devices," *European Polymer Journal*, 2003; vol. 39, no. 9, pp. 1741–1771.
17. Brana MF, Dominguez G, Saez B, Synthesis and anti-tumor activity of new dendritic polyamines- (imide-DNA-intercalator), 2002; 37(7): 541-551.
18. Pushkar S, Philip A, Pathak K, Pathak D, Dendrimers: Nanotechnology Derived field, *Polymers in Drug Delivery. Indian Journal of Pharmaceutical Education and Research*, 2006; 40(3), 153-158.
19. Tomalia DA, Naylor AM, Goddard WA, Starburst Dendrimers: Molecular- Level Control of Size, Shape, Surface Chemistry, 1990; 29(2), 138-175.
20. Yasukawa T, Ogura Y, Tabata Y, Kimura H, Wiedemann P, Honda Y, Drug delivery systems for vitreo retinal diseases. *Progress in Retinal and Eye Research*, 2004; 23(3), 253–281.
21. Hodge P: Polymer science branches out. *Nature* 1993, 362: 18–19.
22. Frechet JMJ, Tomalia DA: *Dendrimers and Other Dendritic Polymers*. Chichester: Wiley; 2001.
23. Newkome GR, Moorefield CN, Vögtle F: *Dendrimers and Dendrons: Concepts, Syntheses, Applications*. Wiley: Weinheim; 2001.
24. Majoral JP, Caminade AM: Dendrimers containing heteroatoms (Si, P, B, Ge, or Bi). *Chem Rev* 1999, 99: 845–880.
25. Bosman AW, Janssen HM, Meijer EW: About dendrimers: structure, physical properties, and applications. *Chem Rev* 1999, 99: 16.
26. Tomalia DA: Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic organic chemistry. *Aldrichimica Acta* 2004, 37: 39–57.
27. Tomalia DA: Dendrimer molecules. *Sci Am* 1995, 272: 62–66.
28. Z. Lyu, L. Ding, A. Y. T. Huang, Poly(amidoamine) dendrimers: covalent and supramolecular synthesis, *Material today chemistry* 2019; 13: 34-48.
29. Basavaraj. K Nanjwade, Hiren M. Bechra, et al, Dendrimers : Emerging polymers for drug delivery systems, *European journal of pharmaceutical sciences* 2009; 38(3): 185-196.
30. Sakthivel T, Florence AT. Dendrimers and dendrons: facets of pharmaceutical nanotechnology, *Drug delivery technology*, 2003; 73-8.

31. D' Emanuele A, R. Jevprasephant. The use of a dendrimer –propranolol prodrug to bypass efflux transporters and enhance oral bioavailability, *Journal of controlled release*, 2004; 95:447-453.
32. Ravindra V Movliya,Pravinkumar M.Patel, Role of Dendrimer in Drug Solubilization - A Review,*Drug delivery letters* 2019;9(4):265-276.
33. . Parajapati Sunil Kumar, Maurya Sheo Datta, Das Manas Kumar, et'al,Potential application of Dendrimers in Drug Delivery :A concise review and update,*Journal of Drug Delivery and Therapeutics* 2016;6(2):71-88.
34. . Kanika Madaan, Sandeep Kumar, Neelam Poonia, Viney Lather,¹ Deepti Pandita. Dendrimers in drug delivery and targeting: Drug-dendrimer interactions and toxicity issues, 2014; 6(3): 139–150.
35. N.Malik, R. Duncan, Dendritic palatinated drug delivery system, NCBI,2003.
36. Wiwattanapatapee R, Lomlim L, Saramunee K. Dendrimers conjugates for colonic delivery of 5-aminosalicylic acid. *J Control Release*. 2003;88:1–9
37. Beezer AE, King AS, Martin IK, Mitchel JC, Twyman LJ, Wain CF. Dendrimers as potential drug carriers; encapsulation of acidic hydrophobes within water soluble PAMAM derivatives. *Tetrahedron*. 2003;59:3873–80.
38. Chauhan AS, Sridevi S, Chalasani KB, Jain AK, Jain SK, Jain NK, et al. Dendrimer-mediated transdermal delivery: Enhanced bioavailability of indomethacin. *J Control Release*. 2003;90:335–43.
39. D'Emanuele A, Jevprasesphant R, Penny J, Attwood D. The use of a dendrimer-propranolol prodrug to bypass efflux transporters and enhance oral bioavailability. *J Control Release*. 2004;95:447–53.
40. Yang H, Lopina ST. Extended release of a novel antidepressant, venlafaxine, based on anionic polyamidoamine dendrimers and poly (ethylene glycol)-containing semi-interpenetrating networks. *J Biomed Mater Res A*. 2005;72:107–14.
41. Prajapati RN, Tekade RK, Gupta U, Gajbhiye V, Jain NK. Dendrimer-mediated solubilization, formulation development and *in vitro-in vivo* assessment of piroxicam. *Mol Pharm*. 2009;6:940–50.
42. Cheng Y, Man N, Xu T, Fu R, Wang X, Wang X, et al. Transdermal delivery of nonsteroidal anti-inflammatory drugs mediated by polyamidoamine (PAMAM) dendrimers. *J Pharm Sci* 2007;96:595-602.
43. Myc A, Majoros IJ, Thomas TP, Baker JR., Jr Dendrimer-based targeted delivery of an apoptotic sensor in cancer cells. *Biomacromolecules*. 2007;8:13–8.
44. Vandamme TF, Brobeck L. Poly (amidoamine) dendrimers as ophthalmic vehicles for ocular delivery of pilocarpine nitrate and tropicamide. *J Control Release* 2005;102:23-38.
45. Tao X, Yang YJ, Liu S, Zheng YZ, Fu J, Chen JF. Poly (amidoamine) dendrimer-grafted porous hollow silica nanoparticles for enhanced intracellular photodynamic therapy. *Acta Biomater*. 2013;9:6431–8.
46. Gupta U, Dwivedi SK, Bid HK, Konwar R, Jain NK. Ligand anchored dendrimers based nanoconstructs for effective targeting to cancer cells. *Int J Pharm*. 2010;393:185–96.
47. Yang W, Barth RF, Wu G, Tjarks W, Binns P, Riley K. Boron neutron capture therapy of EGFR or EGFRvIII positive gliomas using either boronated monoclonal antibodies or epidermal growth factor as molecular targeting agents. *Appl Radiat Isot*. 2009;67:S328–31.
48. Holden CA, Tyagi P, Thakur A, Kadam R, Jadhav G, Kompella UB, et al. Polyamidoamine dendrimer hydrogel for enhanced delivery of antiglaucoma drugs. *Nanomedicine* 2012;8:776-83.
49. Bosnjakovic A, Mishra MK, Ren W, Kurtoglu YE, Shi T, Fan D, et al. Poly (amidoamine) dendrimer-erythromycin conjugates for drug delivery to macrophages involved in periprosthetic inflammation. *Nanomedicine* 2011;7:284-94.
50. Wu G, Barth RF, Yang W, Kawabata S, Zhang L, Green-Church K. Targeted delivery of methotrexate to epidermal growth factor receptor-positive brain tumors by means of cetuximab (IMC-C225) dendrimer bioconjugates. *Mol Cancer Ther*. 2006;5:52–9.

51. Devarakonda B, Li N, de Villiers MM. Effect of polyamidoamine(PAMAM) dendrimers on the in vitro release of water-insoluble nifedipine from aqueous gels. *AAPS PharmSciTech* 2005;6:E504-12.
52. Pandita D, Santos JL, Rodrigues J, Pêgo AP, Granja PL, Tomás H. Gene delivery into mesenchymal stem cells: A biomimetic approach using RGD nanoclusters based on poly (amidoamine) dendrimers. *Biomacromolecules*. 2011;12:472–81.
53. Pasut G, Scaramuzza S, Schiavon O, Mendichi R, Veronese FM. PEG-epirubicin conjugates with high drug loading. *J Bioact Compat Polym*. 2005;20:213–30.
54. Sideratou Z, Kontoyianni C, Drossopoulou GI, Paleos CM. Synthesis of a folate functionalized PEGylated poly (propylene imine) dendrimer as prospective targeted drug delivery system. *Bioorg Med Chem Lett*. 2010;20:6513–7.
55. Dutta T, Garg M, Jain NK. Targeting of efavirenz loaded tuftsin conjugated poly (propyleneimine) dendrimers to HIV infected macrophages in vitro. *Eur J Pharm Sci* 2008;34:181-9.
56. Volha Dzmitruk, Dzmitry Shcharbin, Elzbieta, et al., Dendrimers in anti-HIV therapy. 2011.
57. Morgan MT, Carnahan MA, Immoos CE, Ribeiro AA, Finkelstein S, Lee SJ, et al. Dendritic molecular capsules for hydrophobic compounds. *J Am Chem Soc* 2003;125:15485-9.
58. Kumar PV, Asthana A, Dutta T, Jain NK. Intracellular macrophage uptake of rifampicin loaded mannosylated dendrimers. *J Drug Target* 2006;14:546-56.

