WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 8, 638-659. Review Article ISSN 2277– 7105

DENDRIMER ARCHITECTURE: A COMPREHENSIVE REVIEW

Punya Prakash*, Krishnananda Kamath Kunjal and A. R. Shabaraya

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete Post, Mangalore, Karnataka, India-574143.

Article Received on
13 May 2021,

Revised on 03 June 2021,
Accepted on 23 June 2021

DOI: 10.20959/wjpr20218-20915

***Corresponding Author**
Punya Prakash
Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Farangipete Post Mangalore, Karnataka, India-574143.

ABSTRACT

Dendrimers are an unique kind of polymer. They are monodisperse macromolecules with a lot of branches. Dendrimers structural advantages enable them to play a key role in nanotechnology, pharmaceutical, and medicinal chemistry. Dendrimers are ideal for a wide range of biological and industrial applications due to their unique behaviour. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached that is conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic uses. Dendrimers features, construction, drug delivery, and potential applications in numerous fields of study, technology, and therapy are all highlighted in this review. Recent breakthroughs in simplifying and improving dendrimer synthesis have resulted in a wide range of structures with lower manufacturing costs. In addition, as study improves, newer applications of dendrimers will emerge and the future should witness an higher numbers of commercialized dendrimer based drug delivery systems.

KEYWORDS: Dendrimer, polymer, monodisperse, drug delivery.

INTRODUCTION

Traditional polymer chemistry and technology has focused on linear polymers, which are widely used. Only a few smaller or longer branches can be found in linear macromolecules. It has recently been discovered that the characteristics of highly branched macromolecules differ significantly from those of normal polymers. The structure of these materials has a big influence on how they're used.[1] The name dendrimer comes from the Greek word dendron, which means "tree." ‘Arborols' (from the latin word ‘arbour', which also means ‘tree') and

'Cascade molecule' are synonyms for Dendrimer.[2] Dendrimers are repetitively branched molecules with a monomer unit connected core, resulting in a monodisperse, tree-like, star-shaped molecule with diameters ranging from 2 to 10 nm. A dendrimer is a macromolecule that is distinguished by its highly branched three-dimensional structure, which gives a high level of surface functionality and adaptability.[3] Dendrimers constitute a significant advancement in synthetic chemistry.[4] Dendrimers have customizable interior cavities, surface moieties, sizes, molecular weights, and solvent interactions, allowing them to provide uniform or discrete functions.

Nanoparticle drug delivery systems have gained popularity as a result of their capacity to improve therapeutic agent stability and selectivity. The usage of these nanostructures is limited by drug leakage, cytotoxicity, immunogenicity, hemolytic toxicity, and hydrophobicity in the reticuloendothelial system (RES). Surface engineering dendrimers such as polyester dendrimer, citric acid dendrimer, argining dendrimer, glycol dendrimers, PEGlyated dendrimers, and others can solve these challenges. Bioactive compounds may be readily encapsulated in the inside of dendrimers and chemically attached, such as conjugated, or physically absorbed onto the dendrimer surface, tailoring the carriers desirable features to the specific demands of the active material and its therapeutic uses.[5]

Dendrimers have proven to be effective additions in a variety of drug delivery routes due to their potential to increase drug water solubility, bioavailability, and biocompatibility. These carriers have well-defined molecular weights and trapping characteristics for both hosts and guests. Because dendrimers are made up of branched monomer units that are put together in a stepwise manner, it's feasible to fine-tune molecule size, shape, dimension, density, polarity, flexibility, and solubility by varying the branching units and surface functional groups.[6]

History

Fritz Vogtle in 1978, R.G. Denkewalter at Allied Corporation in 1981, Donald Tomalia at Dow Chemical in 1983 and 1985, and George Newkome in 1985 were the first to synthesis dendrimers using divergent synthesis techniques. Jean Frechet presented a convergent synthetic technique in 1990.

The first synthesized dendrimers were polyamidoamines (PAMAM). At the same time Newkome group independently reported synthesis of similar macromolecules they called 'arborols' [1] The first focus of dendrimer research, according to Tomalia and coworkers, was

on the synthesis, characterisation, and attributes of perfect dendrimers of higher generations. Two fundamentally distinct methodologies, the divergent approach and the convergent approach, were used to synthesise dendrimers produced by step-by-step sequences.[1]

Structure of dendrimer

Dendrimers are monodisperse, three-dimensional, hyperbranched structures with a central core surrounded by peripheral groups. Their physicochemical and biological qualities are dependent on these qualities. Dendrimers often have three distinct architectural components, as seen in the figure 1.

(i) Core;

(ii) Branches (an interior layer composed of repeating units attached to the core) and

(iii)Terminal groups attached to the branches.[6]

The dendritic polymer arrangement creates internal cavities, in which the drug can be deposited, enhance its solubility and stability. The referred characteristics turn these macromolecules into good candidates for pharmaceutical excipients.[4]

Dendrimers start with a nitrogen atom, to which carbon and other elements are added in a sequence of chemical processes that result in a spherical branching structure. As the procedure continues, further layers are added, and the sphere can be extended to the investigator's desired size. The end product is a spherical macromolecular structure that resembles blood albumin and haemoglobin in size.[1]

Properties of dendrimer

Monodispersity

Dendrimers are monodisperse particles that are all the same size. In contrast to linear molecule synthesis, which generates random structure and significant size variation, dendrimer synthesis is well regulated. Dendrimers made using a convergent approach have a higher monodispersity than those made using other methods. Because of incomplete reactions and steric hinderance issues, the majority of structural defects develop during the production of high generation dendrimers.[2]

Monodispersibility has the benefit of being able to anticipate their pharmacokinetic behaviour in a biological organism. One of the most essential elements to consider for a successful dendrimer pharmaceutical use is its pharmacokinetic characteristics. The pharmaceutical

business, for example, uses pharmacokinetic data to choose the best medicine for a certain disease, the vehicle, and the route of administration, with the goal of achieving the best therapeutic response with the least amount of toxicity.[7]

Solubility

Small acidic hydrophobic compounds having antifungal or antibacterial activities can be bound and solubilized by water soluble dendrimers. Unimolecular micelles are dendrimers with a hydrophobic core and a hydrophilic surface. Dendrimers, unlike typical micelles, lack a crucial micelle concentration.This property allows for the encapsulation of poorly soluble pharmaceuticals within the dendritic framework at all dendrimer concentrations, allowing them to be soluble.[3] Dendrimer solubility is determined by the functional group present on the surface. In a polar solvent like water, the hydrophilic group on the surface dissolves. Surface hydrophobic group soluble in non-aqueous solvent The hydrophobic medication is carried in the internal cavity, which promotes solubility. The solubility of dendritic polyester was shown to be much greater than that of comparable linear polyester in a solubility test using tetrahydrofuran as the solvent.[8]

Defined architecture, Size and Shape control

Dendrimers build amplified three-dimensional structures with highly ordered topologies in a highly predictable manner. This characteristic is useful for things like protein modelling and catalysis. Varied molecular sizes have different pharmacokinetics, thus size management is also essential in therapeutic applications.[8] Other dendritic polymers, such as dendronised polymers or hybrid linear-dendritic structures, may have greater potential for certain medical applications than pure dendrimers,but the ability to deliver a pure product will be a key requirement for biological applications; thus, hybrid dendritic structures for such applications will typically begin with dendrimer construction and then hybridise. Dendrimer shape persistence is critical because it allows for the precise positioning of functions not only on the surface of the dendrimer but also within the dendritic scaffold. This is critical for a variety of applications, including sensing. Dendritic structures with distinct holes or voids are also found in stiff dendritic structures. This is necessary for the dendrimer and integrated guest molecules to have specified interactions.[8]

Pharmacokinetic properties

One of the most important things to consider for effective biological applications of dendrimers, such as drug administration, imaging, photodynamic treatment, and neutron

capture treatment, is their pharmacokinetic characteristics.[9] Dendrimers have a wide range of possible uses in medicine, which has sparked increased interest in the field.

Low viscosity

Low viscosity is one of the most significant characteristics of dendritic macromolecules. Dendrimers have a much lower viscosity in solution than 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 helpful because it makes the production of the dendrimer–drug combination easier, and it allows for faster drug release.[4]

Membrane interaction

Some researchers have discovered that cytotoxicity is strongly linked to the terminal groups on the dendrimer's surface. Lee and Larson showed that these cationic nanostructures interact with the negative charges of the phosphate groups of the lipid bilayer via electrostatic interactions, resulting in the creation of tiny holes (nanopores) that contribute to cellular permeability by lowering stability. As a result of the enhanced permeability of the membrane, the spheroidal shape of dendrimers appears to be more efficient in drug transport than linear polymers.[10]

Rheological property

Dendrimers, on the other hand, create a closely packed ball that impacts the rheological characteristics of linear chains in solution. The viscosity of a dendrimer is lower than that of a linear polymer. Intrinsic viscosity increases with increasing molecular mass up to the fourth generation dendrimer, then declines.[2]

Multivalent surface

Dendrimers have the feature of multivalence, which is an essential trait that makes them a suitable excipient. Multivalency, also known as polyvalency, refers to the amount of reactive zones (terminal groups) on a dendrimer's surface that allow it to interact with biological receptor sites including proteins, polymers, cells, and viruses. Dendrimers with modified surfaces might be designed to imitate biological exo-receptors, substrates, cofactors, or

inhibitors. Using cross-linking agents, free surface groups can create complexes or conjugates with medicines or ligands. In general, these interactions are reversible and occur in both biological process inhibition and activation. Multivalent contact, in contrast to weak monovalent receptor–ligand binding, may enhance signal transmission. The increased affinity and cooperativity between the receptor and the ligand is the cause of this enhancement.[11]

Advantages of dendrimers

Compared to other polymers, dendrimers have a number of advantages

- Dendrimers have nano-scopic particle sizes ranging from 1 to 100 nm, making them resistant to reticulum endothelial absorption.
- Due to strict control during synthesis, they have a reduced poly-dispersity index. As branch density rises, the outermost branches form spheres around a lower density core, and the outer surface density rises, yet most of the space stays hollow as it approaches the core. This area has the potential to be used for drug entrapment.
- Dendrimers have several functional groups on their outer surface that may be utilised to connect vector devices for targeting to specific locations in the body.
- Dendrimers can be changed to act as triggers for the release of a medication.
- Dendrimers may have a higher permeability and retention impact than tiny compounds, allowing them to target tumour cells more efficiently.
- They can be synthesised and tailored to individual needs. They are great drug delivery systems due to their possible structure, functionality, and dimensions; moreover, their size is extremely similar to many key biological polymers and assemblies such as DNA and proteins, which are physiologically perfect.[12]

Disadvantages

- Because the drug–dendrimer combination does not penetrate the gut wall, it is not appropriate for oral drug administration.
- Because the drug–dendrimer construct is regarded as a novel chemical entity, clinical testing for the new construct is necessary.[13]

Synthesis of dendrimer

Dendrimers are primarily synthesised using two methods: molecular chemistry and a stepwise controlled approach for preparing dendritic molecules. The second technique is the polymer technique, which involves repeated branching from a monomer core.[17] PAMAMs

were the first synthetic dendrimers, announced in 1980. Later years saw the development of additional dendrimers such as poly(propyleneimine) (PPI) and poly-L-lysine (PLL), glycodendrimers, polyester dendrimers, and amphiphilic dendrimers.[14]

Dendrimers can be synthesized by the following methods:

Classical synthesis pathways

Dendrimers are often made using techniques that allow for structural control at every step of the process. Dendritic structures are typically created using one of two methods: divergent or convergent.[4]

Divergent growth method

The divergent growth approach was the first to be proposed, and it remains the most used today. This is one of the earliest techniques, in which the synthesis starts at the centre and spreads outwards by repeating the two fundamental reactions.

a) The monomer's coupling.
b) Changing the end group of the monomer to provide a new coupling site for the following monomer

The divergent growth technique (fig 2) consists of repeating the two preceding procedures until the necessary dendrimer production is obtained. The divergent processing begins with the activation or alteration of the core and the coupling of the first monomer, resulting in the dendrimer's initial generation. 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. A new generation corresponds to the number of branched layers from the core when a new layer of branching units is produced. To avoid deficiently produced branches in the divergent method, it is critical that each phase of the reaction be fully finished before adding a new generation.[15] 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.

The divergent method usually results in the production of extremely symmetric dendrimer molecules. However, researchers have lately explored the idea of using the divergent growth approach to generate heterogeneously functionalized dendrimers, resulting in dendrimers with a variety of functional groups attached to the groups.[16]

Convergent process

The convergent process, introduced by Fréchet and Hawker in 1989–1990, is an alternate technique for the synthesis of dendrimers. The convergent technique, in contrast to the divergent approach, synthesises dendrimers from what would eventually become the structure's exterior, i.e. the surface, rather than the core.

In order to achieve the required dendritic structure, the convergent growth technique (fig 3) also involves repeating the coupling and activation stages. The surface groups, which are usually two, are first linked to a monomer to form the dendritic segment (dendron generation zero). The second step is to activate this fragment so that it may create a first-generation dendron, or dendritic wedge, by combining it with other monomers. This synthetic method may be repeated to produce bigger generation dendrons, which may then be linked to a multifunctional core in the last phase to produce the final dendrimer. In the core, two or more dendrons are joined together to create the dendrimer, completing the convergent synthesis process. Because the coupling process takes place near the developing dendron's focus point, steric inhibition makes the production of big dendrimers (typically above the sixth generation) more difficult,resulting in lower yields.[4]

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. Multiple attaching groups are connected with branched monomers, along with a synthesis of blocks by focal point establishment, which are then linked with a hyper core to synthesise a higher generation of dendrimers, develops the hyper core, which consists of multiple attaching groups are connected with branched monomers, along with a synthesis of blocks by focal point establishment, which are then linked with a hyper core to synthesise a higher generation of dendrimers.[17] As seen in figure 4.

Double Exponential and Mixed growth

The idea and consequences of 'double exponential' growth were the most recent fundamental advance in the practise of dendrimer synthesis. An AB2 monomer having orthogonal protecting groups for the A and B functions is used in double exponential growth, which is analogous to a fast growth method for linear polymers. This method permits monomers to be produced from a single starting material for both convergent and divergent development. When these two products are combined, an orthogonally protected trimer is formed, which

may be utilised to repeat the growth process. The power of double exponential growth is more subtle than the capacity to construct huge dendrimers in a limited number of steps. In fact, double exponential growth As seen in figure 5 is so quick that it can only be repeated two or three times before it becomes impossible to expand further. The double exponential technique allows a dendritic fragment to be expanded in either a convergent or divergent manner, depending on the situation. In this way, the benefits of both systems may be accessible without having to acknowledge their flaws.[8]

Orthogonal coupling strategy

It's a fast synthesis technique that skips the deprotection and intermediate activation stages, resulting in dendrimer development that's much faster. The chemoselective reaction between the monomers is involved.

Click chemistry

When compared to other reactions, click chemistry is one of the most significant and leading processes. It is not enough to finish or swap 95 percent of the chemistry to produce higher generations of dendrimers. Because maintaining purity in a stepwise procedure is difficult, monodispersity of a dendrimer is seen.[17] Click reactions such as Copper-Assisted Azide-Alkyne Cycloaddition (CuAAC), Thiol-ene and Thiol-yne Click Reactions (TEC TYC), and Diels-Alder (DA) Reaction have been used to synthesise dendrimers. Click chemistry application using an effective coupling agent to combine the medication with the PEGylated PAMAM dendrimer to improve polymer-drug coupling efficiency.[18]

Lego chemistry

It's a two-branched monomer-based direct synthesis technique in which each quantitative step corresponds to a generation (5 steps will give a fifth-generation G5 dendrimer). Only environmentally beneficial by-products such as sodium chloride, water, nitrogen, and other elements will be produced. It is also a cost-effective and time-saving approach.[19]

Factors affecting dendrimer properties

Effect of pH

The structural behaviour of PAMAM dendrimers is affected by pH. At low pH, the interior becomes increasingly empty.[4] Repulsion between positively charged amines on the dendrimer surface and tertiary amines in the interior increases as production increases.

At neutral pH, back-folding occurs, which might be owing to hydrogen bonding between the molecule's uncharged tertiary amines. When the molecule's charge becomes neutral at a higher pH (pH>10), the dendrimer compresses, resulting in a more spherical (globular) form with the least number of repulsive interactions between the dendrimer arms and between the surface groups.[2]

Dendrimers and The effect of salts

High ionic strength, i.e., high salt concentration, has a substantial influence on charged dendrimers like PPI, favouring a constricted conformation of dendrimers with a high degree of back-folding, similar to what is seen when pH is increased. To minimise charge repulsion on the structure, the repulsive interactions between the charged dendrimer segments result in a stretched form at low salt concentrations.[20]

Effect of solvent

With diminishing solvent quality, i.e. decreased solvation, dendrimers of all generations undergo a greater degree of back folding. Low generation dendrimers, on the other hand, have a larger tendency to back-fold owing to insufficient solvation than higher generation dendrimers since they are more flexible.[8]

When examining the conformational state of a dendrimer, the capacity of the solvent to solvate the dendrimer structure is a crucial parameter.[8] The capacity of any solvent to solvate the dendrimer is an important consideration. Dendrimers of all generations show more back-folding as the solvent quality decreases. The dendrimer arms increase the molecular density of the dendrimer surface. Nonpolar solvents, such as benzene, solvate PPI dendrimers poorly, favouring intramolecular contacts between dendrimer segments and back-folding, according to NMR studies.[2]

Effect of concentration of dendrimer

Experiments with PPI dendrimers (G4, G5) in a polar solvent like methanol using small angle X-ray scattering (SAXS) show that the molecular arrangement of dendrimers shrinks with increasing concentration.[2]

Mechanism of drug delivery through dendrimers

Dendrimers can operate as drug carriers by encapsulating pharmaceuticals inside the dendritic structure or by interacting with medicines via electrostatic or covalent interactions

at their terminal functional groups (prodrug). Drug distribution may be divided into two types[21]

1. Drug molecules can be physically entrapped within the dendritic structure, which are given in (Figure 6)
2. Drug molecules can be covalently linked onto the dendrimer surface (or) other functionalities to produce dendrimer-drug conjugate, which are given in (figure 7).

Modes of drug encapsulation in dendrimers

The kind of dendrimer and core moiety employed determines the drug release phenomena. Physical encapsulation, electrostatic encapsulation, and covalent conjugation are all examples of drug release mechanisms.[22]

Physical encapsulation

Due to alterations in their form, cavities, and structural designs, the guest molecules were entrapped in the macromolecule's inner moiety in this approach. Internal cavities stay empty due to two types of contacts lipophilic and hydrophobic contacts, which produce interactions with medicinal molecules containing nitrogen or oxygen atoms and the release of the hydrogen bond. Hydrogen bonding occurred as a result of a variety of interactions, including physical and hydrogen bonding.[22]

Electrostatic interactions

The interaction in this technique of encapsulation occurs on the surface of dendrimers, which include a high number of NH2 and COOH groups that are utilised to increase the solubility of lipophilic medicaments. Ibuprofen, ketoprofen, diflunisal, naproxen, and indomethacin, all of which are readily ionizable, form complexes with the multifunctional surfaces of dendrimers containing terminal groups.

Covalent conjugation

This conjugation technique is utilised for compounds with functional groups on their exterior surface. The conjugation is accomplished by the chemical and enzymatic breakdown of hydrophilic labile bonds in this technique. Apart from that, the medicines can be conjugately linked using a spacer such as polyethylene glycol paminobenzoic acid, p-aminohippuric acid, or lauryl chains; the drug's stability and kinetics are improved by using a spacer. Penicillin V, venlafaxine, 5-aminosalicylic acid, naproxen, and propranolol are only a few examples of

drugs conjugated with PAMAM dendrimers. As a result, the solubility and controlled release of pharmaceuticals are improved.[7]

Types of dendrimer

Table 1 lists a types of dendrimers with various functionalities.

Formulation of dendrimers

Different types of products are formulate by using Dendrimers and some dendrimer based products are given in Table 2.[1]

Application of dendrimer

Dendrimers are useful for a range of high-tech applications due to features such as unrivalled molecular homogeneity, multifunctional surfaces, and the existence of interior voids.

Pharmaceutical application

Ocular drug delivery

The creation of ophthalmic vehicles for ocular drug administration utilising PAMAM dendrimers for pilocarpine nitrate was reported by Vandamme and Broberck. Using PAMAM dendrimers, they discovered that there is greater ocular residence time and considerably improved bioavailability.[23] Nonirritating, serial, isotonic, biocompatible, does not run out of the eye, and biodegradable are all desirable qualities in an ocular medication delivery method. Dendrimers offer a one-of-a-kind answer to the problem of ocular medication delivery. PAMAM dendrimers with a carboxyl hydroxyl surface group were used. Recent research attempts to improve pilocarpine's in-eye residency duration have increased. By adding PEG groups to the dendrimer, it is possible to synthesis hydrogels that increase the volume in aqueous solution and are more comparable to biological tissue. These hydrogels are used in the synthesis of cartilage and the closure of ocular lesions. In ocular drug molecules, a hydrogel consisting of PEGlyated dendrimers attaches to the dendrimer and transports the drug to the eye efficiently.[5]

Dendrimers in pulmonary drug delivery

Dendrimers have also been used to transport drugs to the lungs. Measurement of plasma anti-factor Xa activity employing PAMAM dendrimers in increasing pulmonary absorption of Enoxaparin and observation of preventive efficacy of deep vein thrombosis in a rat model were used in one of the research. Positively charged G2 and G3 generation PAMAM

dendrimers improved the relative bioavailability of Enoxaparin by 40%, but negatively charged carboxylic groups in G2.5 PAMAM half generation dendrimers had no impact. As a result, positively charged dendrimers are a good vehicle for delivering Enoxaparin to the lungs.[6]

Dendrimers in oral drug delivery

Because of its simplicity of manufacture and low cost design of dose, oral medication administration is the most common and has gained increasing attention in the pharmaceutical sector. Oral medication distribution is influenced by a number of factors, including the kind of delivery method, the condition being treated, the patient, the length of therapy, and the medication's characteristics. In the regulation of medication release rate, controlled release systems for oral use are mostly solids and rely on dissolving, diffusion, or a combination of both processes.[23] One major advantage of oral drug administration is that with controlled drug delivery systems, the drug is progressively released from the dose and maintains a consistent blood level, resulting in fewer changing plasma drug levels. Along with its benefits, oral administration has certain drawbacks, such as poor solubility in aqueous solutions and limited penetration through intestinal membranes.[18]

Dendrimer in transdermal drug delivery

Transdermal drug delivery is the administration of a medication via the skin to produce a systemic impact. The medication is transported via the dermal and epidermal tissues of the skin in this scenario for a local therapeutic impact. The therapeutic usage of NSAIDs is limited due to adverse responses such as GI and renal side effects when taken orally. Transdermal medication administration overcomes these negative effects while also maintaining therapeutic blood levels for a longer length of time. Transdermal delivery suffers from a low rate of transcutaneous distribution due to the skin's barrier function. Dendrimers are a suitable choice in this sector since they include hydrophobic moieties and have a poor solubility property.[5]

Dendrimers in Targeted and Controlled release drug delivery

Dendrimers make it easier to passively target drugs to solid tumours. Because of their increased solubility and plasma circulation time, this is the case. EPR (Enhanced Permeation and Retention) in tumour tissues reduces anticancer medication cytotoxicity and increases cancer cell line uptake.[23]

Dendrimers in gene delivery

In gene therapy, dendrimers can be used as vectors. PAMAM dendrimers have been investigated as carriers of genetic material. Several studies have described the use of amino-terminated PAMAM or PPI dendrimers as nonviral gene transfer agents, increasing DNA transfection via endocytosis and, eventually, into the cell nucleus.[1]

Dendrimer as solubility enhancer

Dendrimers are unimolecular micellar in nature, with hydrophilic exteriors and hydrophilic interiors that form covalent and non-covalent interactions with drug molecules and hydrophobes, improving solubility.[24]

Cellular delivery using dendrimer carrier

Dendrimer– ibuprofen complexes entered the cells quickly compared to pure drug(1hr versus>3 hr), suggesting that dendrimers can efficiently transport the complexes medication into cells.[24]

Dendrimers as Nano-Drugs

When Poly(lysine) dendrimers modified with sulfonated naphthyl groups are used as antiviral medicines against the herpes simplex virus, they might potentially prevent/reduce transmission of HIV and other sexually transmitted illnesses (STDs). PPI dendrimers with tertiary alkyl ammonium groups attached to the surface, as well as Chitosan–dendrimer hybrids, show potent antibacterial biocides against Gram positive and Gram negative bacteria when used as antibacterial agents, carriers in drug delivery systems, and other biomedical applications.[24]

Dendrimers as bio mimetic artificial proteins

Due to their dimensional length scaling, limited size distribution, and other biomimetic characteristics, dendrimers are sometimes referred to as "artificial proteins." PAMAM dendrimers, for example, closely match the sizes and contours of several key proteins and bio assembly, such as insulin (3 nm), cytochrome C (4 nm), and haemoglobin (5.5 nm), which are all around the same size and shape as ammonia-core PAMAM dendrimers generations 3, 4, and 5.[24]

Dendrimers as nano-scaffolds

Due to an excellent platform given by the dendrimer surface for the attachment of cellspecific ligands, solubility modifiers, and stealth molecules, the interaction with macromolecules from the body defence system and imaging tags is reduced. Folate PAMAM dendrimers, for example, have been effectively utilised as carriers of boron isotopes in the treatment of cancer tumours using boron neutron capture.

Therapeutic application

Dendrimers for boron neutron capture therapy (BNCT)

The radiation produced by the capture reaction of low energy thermal neutrons by 10B atoms, which contain roughly 20% natural boron, to release particles and recoiling lithium-7 nuclei is referred to as boron neutron capture treatment (BNCT). This radiation energy has been effectively utilised to destroy tissue selectively. Due to their well-defined structure and multivalent nature, dendrimers are an interesting molecule for use as boron carriers.[25]

Dendrimers in photodynamic therapy (PDT)

Photodynamic treatment (PDT) uses visible or near-infrared (NIR) light to activate a photosensitizing chemical. Excitation produces a highly energy state that, when combined with oxygen, produces highly reactive singlet oxygen capable of causing necrosis and death in tumour cells. In the last several years, dendritic administration of PDT drugs has been studied in order to enhance tumour selectivity, retention, and pharmacokinetics.[9]

Dendritic sensors dendrimers

Despite being single molecules, they can have a lot of functional groups on their surfaces. This makes them stand out in applications where the dendrimers' hydrophilic exteriors and interiors, which account for their unimolecular micelle nature, are required. Dendrimer-based carriers have the potential to improve the oral bioavailability of difficult-to-absorb medicines.[10]

Diagnostic application

To improve the pharmacokinetic characteristics of dendrimer contrast agents, target specific moieties were added to them, such as folate conjugated Gd (III)–DTPA PAMAM dendrimer, which enhanced the longitudinal relaxation rate of tumour cells expressing the high affinity folate receptor.[24]

Dendrimers as X-ray contrast agents

Dendrimers as X-ray contrast agents: The X-ray machine is a basic diagnostic tool in medicine that may be used to diagnose a wide range of illnesses. Several illnesses or organs, such as arteriosclerotic vasculature, tumours, infarcts, kidneys, or efferent urine, need the application of an X-ray contrast agent to generate a high resolution X-ray picture. Dendrimers are being researched as possible polymeric X-ray contrast agents.[25]

Dendrimers as molecular probess

Use as molecular probes due to their unusual shape and distinctive features. Because of their vast surface area and high density of surface functions, immobilising sensor units on the surface of dendrimers, for example, is a particularly effective approach to produce an integrated molecular probe.[26]

Dendritic catalysts/enzymes

Because of their unique form and characteristics, they can be used as molecular probes. Immobilizing sensor units on the surface of dendrimers, for example, is a particularly successful technique for producing an integrated molecular probe due to their large surface area and high density of surface functionalities. Dendritic shells can be utilised to generate a catalysis-friendly microenvironment or to protect functional groups at the dendritic core.[23]

Miscellaneous

Dendrimers based product in cosmetics

Dendrimers have an important role in cosmetics. Dendrimers were utilised in the development of several cosmetics industry [amidoamine] dendrimers as ophthalmic vehicles. L'Oreal holds a patent on the use of dendrimers in cosmetics like mascara and nail paint. Unilever also holds a patent for the use of dendrimers in the manufacture of sprays, gels, and lotions.[23]

Dendrimers in waste water treatment

Water polluted by hazardous metal ions, inorganic solutes, and organic solutes is purified using dendritic polymers.[23]

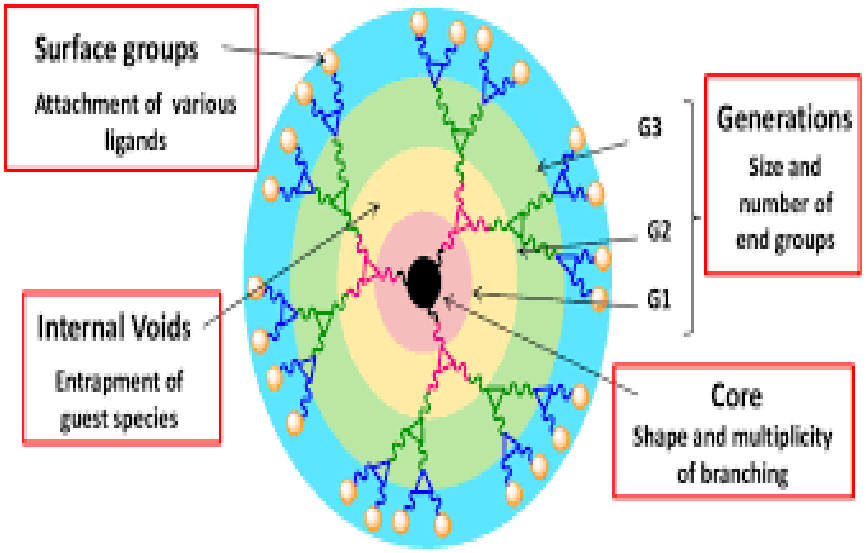

Fig. 1: Structure of dendrimer.

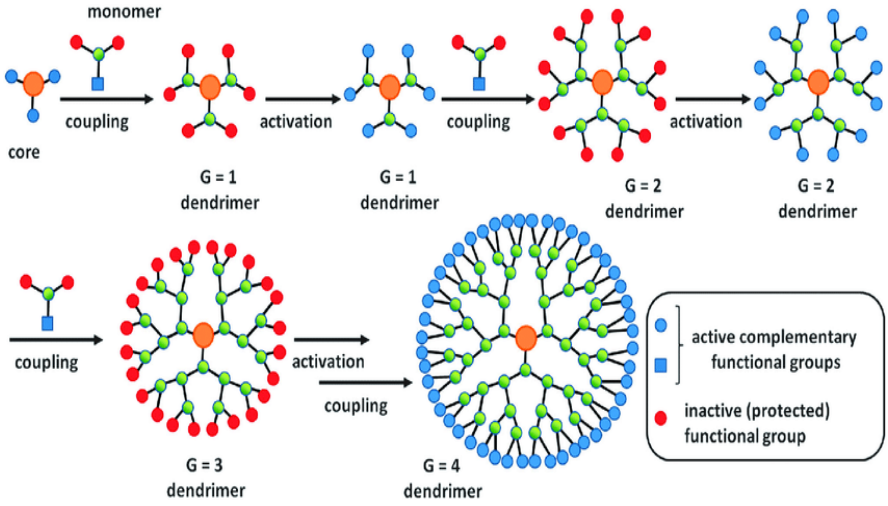

Fig. 2: Divergent synthesis of dendrimer.

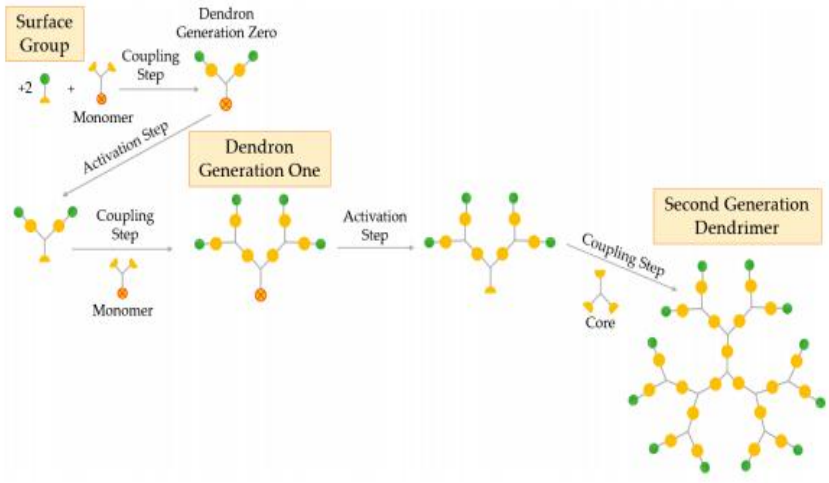

Fig. 3: Convergent synthesis of dendrimer.

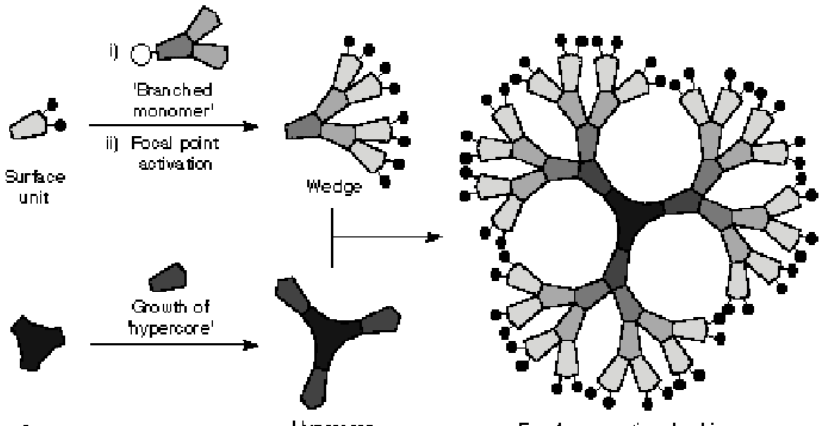

Fig. 4: Hyper cores and branched monomer growth.

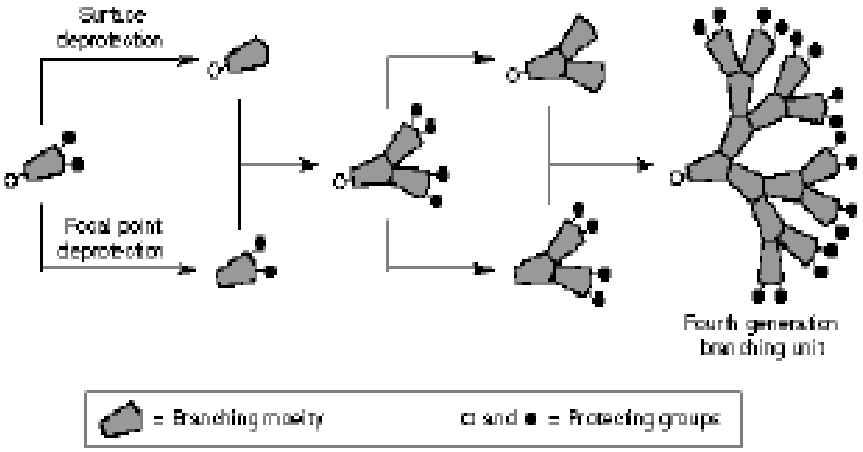

Fig. 5: Double Exponential and Mixed growth.

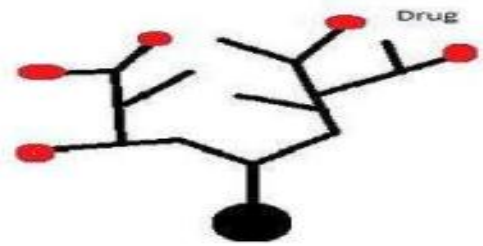

Fig. 6: Dendrimer molecule with drug molecules loaded at terminal surface of branches.

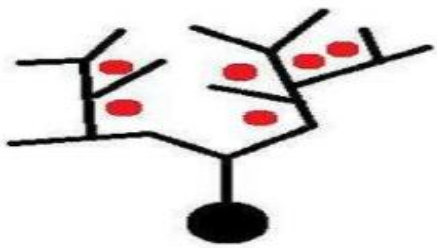

Fig. 7: Dendrimer molecules with drug molecules encapsulated within branches.

Table 1: Types of dendrimer.

Sl. no.	Type of dendrimer	Synthesis	Example	Characteristics
1	PAMAM (Poly Amido Amine) Dendrimer	Divergent	Dendritech TSM (USA)	These are spheroidal or ellipsoidal in shape[24] It has high solubility and reactivity due to incidence of a number of functional end groups and empty internal cavities.[27]
2	PPI (Poly Propylene Imine) Dendrimer	Divergent	Asramolby DSM (Netherlands)	Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as center
3	Chiral Dendrimer	Convergent	chiral dendrimers derived from pentaerythritol	based upon the buildingof constitutionally different but chemically alike branches to chiral core.[28]
4	Multilingual Dendrimers	Convergent	VivaGel	These were made up of core dendrimers, which can be surrounded by other dendrim-ers,whichexecute aspecificfunction leading to a smarttherapeutic system used for diagnose the diseased state.[29]
5	Tecto Dendrimers	Divergent	Mercapto	
6	Hybrid Dendrimers	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes	These dendrimers have characteristic of both dendritic and linear polymer
7	Peptide Dendrimers	Convergent	Beta Casomorphin (human)	Peptide dendrimers are those which hold amino acid as branching or interior unit. These are used for the diagnostic purpose and vaccine deliverys
8	Frechet-Type Dendrimers	Convergent	Frechet type Dendron azides, TM Priostar	These were based on polybenzyl ether hyper branched skeleton. improve the solubility of dendrimers.[30]
9	PAMAMOS(Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergen	SARSOX	These are silicon containing commercial dendrimers
10	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	vaccine and diagnostic research	These are dendron-like molecular assembly based upon a polylysine frame.[31]

Table no. 2: Different formulation of dendrimers.

Sl. no.	Brand name	Types of dendrimer	Application
1	Vivagel	Multiple Antigen	HIV Prevention
2	Alert ticket	PAMAM	Anthrax Detection
3	Startus CS	Tecto	Cardiac Marker
4	Priofect™, Priostar™	Tecto	Targeted diagnostic, therapeutic deliveryfor cancer cells
5	Superfect	Ampiphilic	Gene Transfection

CONCLUSIONS

Dendrimer chemistry advances year after year, and many research organisations and businesses are eager in learning more about their features and prospective applications. The key conclusion is that dendrimers are appropriate carriers for numerous applications such as drug delivery, therapeutic, and diagnostic agents due to their great level of control over their architecture, shape, branching length and density, and surface functioning. Poor solubility, bioavailability, and permeability are all issues that a growing number of medications are encountering today. Dendrimers might be an effective strategy for improving the delivery of such difficult-to-administer medicines. Dendrimer synthesis advances have resulted in a wide spectrum of structures with decreased production costs. Furthermore, because of the high density of surface groups, targeting groups as well as groups that influence dendrimer toxicity or solution behaviour can be attached. As research continues, new applications for dendrimers will emerge, and there should be an increasing number of commercial dendrimer-based drug delivery systems in the future.

REFERENCES

1. Rai AK, Tiwari R, Maurya P, Yadav P. Dendrimers: a potential carrier for targeted drug delivery system. Pharmaceutical and Biological Evaluations, 2016; 3(3): 275-87.
2. Shahi SR, Kulkarni MS, Karva GS, Giram PS, Gugulkar RR. Int. J. Pharm. Sci, 2015; 33(1): 187-198.
3. Mathur V, Satrawala Y, Rajput MS. Dendrimers: A Review. Inventi Impact NDDS, 2015; 1(1).
4. Chen CZ, Cooper SL. Recent advances in antimicrobial dendrimers. Advanced Materials, 2000; 12(11): 843-6.
5. Gorkhe YS, Pande VV, Autade RR. Dendrimers: A Platform for Novel Drug Delivery System. International Journal of Pharmaceutics and Drug Analysis. 2018 Apr 4: 439-45.

6. Agrawal A, Kulkarni S. Dendrimers: a new generation carrier. International Journal of Research and Development in Pharmacy & Life Sciences, 2015; 15, 4(5): 1700-12.
7. Gillies, E.R.; Fréchet, J.M.J. Dendrimers and dendritic polymers in drug delivery. Drug Discov. Today, 2005; 10: 35–43.
8. Kumar BP, Chandiran IS, Bhavya B, U S, M S.Dendrimer: a complete drug carrier. International Journal of Pharmacy Review & Research, 2011; 1(1): 25-39.
9. 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 research letters, 2014; 9(1): 1-0.
10. jain, K.; Kesharwani, P.; Gupta, U.; Jain, N.K. Dendrimer toxicity: Let's meet the challenge. Int. J. Pharm, 2010; 394: 122–142.
11. Prajapati, S.K.; Maurya, S.D.; Das, M.K.; Tilak, V.K.; Verma, K.K.; Dhakar, R.C. Dendrimers in Drug Delivery, Diagnosis and Therapy: Basics and Potential Applications. J. Drug Deliv. Ther, 2016; 6: 67–92.
12. Schumann, H., Wassermann, B.C., Schutte, S., Velder, J., Aksu, Y and Krause, W., Synthesis and characterization of water-soluble tin-based metallodendrimers. Organometallics, 2003; 22: 2034-41.
13. Kakade T, Kadam V, Dhanavade K, Salunkhe V, A review on pharmaceutical nanotechnology: Dendrimer, World journal of pharmacy and pharmaceutical science, 2013; 2: 4815- 4830.
14. Choudhary, S.; Gupta, L.; Rani, S.; Dave, K.; Gupta, U. Impact of Dendrimers on Solubility of Hydrophobic Drug Molecules. Front. Pharmacol, 2017; 8: 1–23.
15. Mendes, L.P.; Pan, J.; Torchilin, V.P. Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy. Molecules, 2017; 22: 1401.
16. Boas, U.; Christensen, J.B.; Heegaard, P.M.H. Dendrimers: Design, Synthesis and Chemical Properties. In Dendrimers in Medicine and Biotechnology. New Molecular Tools; The Royal Society of Chemistry: Cambridge, UK, 2006; 1–27.
17. Chirag M,DV G, Babu S, NK FR. A Comprehensive review on Dendrimers in current advanced Drug delivery. Int. J. Res. Pharm. Sci, 2020; 11(1): 1055-1066
18. SASI S, JOSEPH SK, ARIAN AM, THOMAS S, AMRUTHA V, ARYA G, NAIR SC. An updated review on the application of dendrimers as successful nanocarriers for brain delivery of therapeutic moieties. International Journal of Applied Pharmaceutics, 2021; 7: 1-9.

19. Zolotarskaya OY, Xu L, Valerie K, Yang H. Click synthesis of a polyamidoamine dendrimer-based camptothecin prodrug. RSC Adv, 2015; 5: 58600-8.
20. Ramzi, A.; Scherrenberg, R.; Joosten, J.; Lemstra, P.; Mortensen, K. Structure-property relations in dendritic polyelectrolyte solutions at different ionic strength. Macromolecules, 2002; 35: 827–833.
21. Priya P, Sivabalan M, Jeyapragash R. Dendrimer: A Novel Polymer. IJRPC, 2013; 3(2): 2231-781.
22. Mittal P, Saharan A, Verma R, Altalbawy F, Alfaidi MA, Batiha GE, Akter W, Gautam RK, Uddin M, Rahman M. Dendrimers: A New Race of Pharmaceutical Nanocarriers. BioMed Research International, 2021; 15: 2021.
23. Verma NK, Singh AK, Mall PC, Yadav V, Jaiswal R. Dendrimers and its application: a review. European Journal of Biomedical AND Pharmaceutical sciences, 2020; 7(5): 189-194.
24. Garg T, Singh O, Arora S, Murthy R. Dendrimer—A novel scaffold for drug delivery. Int J Pharm Sci Rev Res, 2011; 7(2): 211-20.
25. Srivastava A, Saxena P, Singh A, Jough SS. Dendrimer-a novel technique for drug delivery, 2017; 6(12): 211-230.
26. Jang WD, Selim KK, Lee CH, Kang IK. Bioinspired application of dendrimers: from bio-mimicry to biomedical applications. Progress in Polymer Science, 2009; 1, 34(1): 1-23.
27. Roseita E, Tomalia DA, Poly (amidoamine)(PAMAM) dendrimers: from biomimicry to drug delivery and biomedical applications. Drug Delivery Today, 2001; 6(8): 427-36.
28. Hawaker C, Wooley KL, Frechet JMJ. Unimolecular micelles and globular amphiphiles: dendritic macromolecules as novel recyclable solubilization agents. Journal of Chemical Society. Perkin Transactions, 1993; 1(12): 1287-9.
29. 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): 153-8.
30. 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): 253–81.
31. Tripathy S, Das MK. Dendrimers and their Applications as Novel Drug Delivery Carriers. Journal of Applied Pharmaceutical Science, 2013; 3(09): 142-9.