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Dendrimers: A potential novel drug carrier

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Abstract

Dendrimers- a novel synthetic polymeric system, comes with unique physicochemical properties due to their exclusive three-dimensional structure. Thus, features like distinct shape, size, monodispersity and the molecular weight is attained. Moreover, it presents compatibility with drug active moieties along with bioactive molecules including heparin, DNA and polyanions, to name a few. The recognition abilities and nanoscopic size make it a remarkable tool for self-assembly and coordination. In addition to this, the internal voids of the dendritic configuration allow the incorporation of hydrophilic and phobic drugs. Yet the end groups are catered for combining the bioactive constituents and antibodies, enabling better reactivity, solubility and miscibility. Currently, dendrimers are a point of interest for the exploration of new routes and to serve as nanocarriers. However, the cationic charge and toxicity are neutralized via PEGylation of dendrimers still keeping its carrier properties intact. The undertaken review comprises numerous properties and structural characteristics of dendrimers and their applications as a potential novel delivery system.

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Introduction

The word “macromolecule” denotes a group of two or more than two molecules, clasped together via intermolecular forces (Singh *et al.*, 2014). Such are dendrimers: macromolecular structures having branched, three dimensional and nano-sized molecules. It comes with multivalent surface functional groups, exhibiting globular and monodisperse nature with synthetically elastic potential and thus, diverse pharmaceutical applications. The word ‘dendrimers’ is derived from two Greek words: “dendron” meaning tree and “meros” meaning parts, depicting the distinctive tree-like aspects of these composites (Tomalia, 2005; Ambekar *et al.,* 2020). Dendritic assemblies are widespread themes in nature and are frequently consumed where a specific function needs to be enhanced. The brain and the central nervous system are one of the best examples of dendritic structure which achieves the largest exchange of information and material with the neighboring tissues (Carmo *et al.,* 2013). Another prominent example of dendritic structures, in nature, is the recently discovered excessive number of foot hair called “setae” on gecko’s feet. These setae form striking dendritic networks of tiny hairs on the foot called a spatula. These spatula-like structures enable the gecko to adhere to surfaces. Manipulation of the structural features of dendrimers permits controlled synthesis of highly branched terminally functionalized macromolecules which describe improved awareness for many potential pharmaceutical applications. With a unique system of dendritic arrangement and synergistic action of each entity, the dendritic configuration greatly improves the total function of the system (Baig *et al.,* 2015).

History of dendrimers

Nature often ends up making dendritic solutions in animals and plants designed to improve specific properties as proved in animal respiratory systems. Likewise, plants utilize their dendritic properties above the ground to increase leaves' exposure to sunlight and beneath the soil, they need to expose a large functional area while accumulating water from the soil. Thus a dendrimer is a distinct nanoparticle as well as a molecule covalently assembled. The very earliest fruitful attempt by divergent synthesis to design and create dendritic structures was approved by Fritz Vögtle and collaborators in 1978. Despite a lot of investigators spending their efforts on bringing advancement in dendrimers applications, scientists still believe that the progress in this area of drug delivery or drug carriers is still in its infancy (Tomalia, 2016).

Structure of dendrimers

As dendrimer propagates from generation to generation, some definite functions are accomplished by each factor with concurrent properties (Carmo and Paim, 2013). The chief central core is the molecular information hub that articulates a certain size, shape, directionality and multiplicity through a covalent bond to the functional groups at the margin (Golshan *et al.,* 2020). Along with the propagation of dendrimer, branched cell amplification or generations defines the volume and type of internal space of void created therein. However, the internal space defines the nature and extent of host-guest properties that can be accomplished in any specific dendrimer family (Fig. 1). The functional groups on the surface are passive or reactive terminal groups that can perform various functions while the majority of dendritic polymers are organic.

Dendrimers which consist of main-group elements or transition metals have been far less considered (Moulines *et al.,* 1993: Newkome *et al.,* 1994; Yamamoto *et al.,* 2019).

Segment and layer block dendrimers

Segment-block dendrimers are fabricated with dendritic fragments of different compositions. These can be obtained by attaching different blocks to one multifunctional core molecule. On the other hand, layer-block dendrimers consist of concentric layers (Caminade and Majoral, 2016). These are the products achieved by placing concentric spheres around the polyfunctional central core. Frechet and Hawker synthesized a segment- block dendritic polymer which had two ester-linked and an ether-

linked segment. They also manufactured a layer block dendrimer for comparison, whose outer three generations were ether-linked and the inner two were ester-linked (Hawker and Frechet, 1992). Great efforts are required to synthesize high generation dendritic polymers in larger quantities via multi-step procedures.

The conception of self-assembly for dendrimer synthesis was applied by Zimmerman's group due to the above-mentioned facts (Zimmerman *et al.,* 1996). With a dendritic tail, a molecule was prepared by them in such a fashion that it could self-assemble to form a cylindrical aggregate of wedge-shaped six subunits. With a large central cavity, this hexameric aggregate was about 2 nm in thickness and 9 nm in diameter. Between carboxylic acid groups, the six wedge subunits are held together by hydrogen bonds attaining stability via Vander Waals forces. It is to note that hexamer stability is affected by several factors like dilution, by placing the aggregate in polar solvent like THF (tetrahydrofuran) while at temperature stability loses with the breakup of aggregate into monomer. Also, the noncovalent nature of hexamer adds to its limited stability (Salvi *et al.,* 2020).

Properties of dendrimers

Some notable properties of dendrimers include (Tomalia *et al.,* 2007):

Sizes of nanoscale with similar dimensions to vital bio-building blocks e.g. DNA, proteins.

Numbers of surface terminal groups (Z) appropriate for drug bio-conjugation, targeting moieties, biocompatibility, or signaling groups.

Functional groups designed surfaces to resist or augment epithelial, vascular, or transcellular bio permeability.

Drugs are encapsulated in interior voids. Small drug molecules or metals are encapsulated in that void area facilitate control drug release and lessens the toxicity of the drug.

Patterns of positive biocompatibility are associated with neutral polar or lower generation anionic terminal surface groups in contrast to higher generation cationic and neutral apolar surface groups. Low or non-immunogenicity related to maximum dendrimer surfaces adapted with polyethylene glycol (PEG) or small functional groups.

Surface terminal groups can be improved to enhance receptor-mediated targeting, controlled release or bio-distribution from the interior void space.

Synthetic routes

Dendrimers are produced by altering the functionality of each component to better properties like thermal stability, allowing the addition of compounds for certain applications, and improved solubility. Dendritic polymers are assembled from a polyfunctional core extended outward by a sequence of reactions termed Michael addition reactions (Serenko *et al.,* 2017). Each reaction step must be driven to the conclusion in schematic order to avoid trailing generations (branches become shorter than others). It is cautionary to avoid any impurities (trailing generations), otherwise, a negative influence on the functionality and symmetry of the dendritic polymers is seen. There are two recognized approaches for dendrimer synthesis, i.e. convergent and divergent techniques, the selection of process for synthesis greatly depends on the application and target end.

Divergent synthesis

At this point, the manufacture of the dendritic polymer occurs in a gradual stepwise style which initiates from the core. It further proceeds by the molecule build-up towards the boundary via two simple processes namely; monomer coupling and monomer end-group transformation to generate a fresh reactive surface for the pairing of a new monomer (Boas *et al.,* 2006). The divergent synthesis starts with a polyfunctional core molecule like EDA (ethylenediamine), followed by the addition of four

arms on the nitrogen of EDA are by Michael addition reaction. Subsequently, in the second phase through amidation reaction, EDA is reacted to four arms.

To form different dendrimer generations, these two phases are repeated numerous times, and the number of arms for each generation doubles from the previous one. At higher generations, to escape structural defects an excess of Michael donor i.e. EDA (ethylenediamine) is used in this method. To get a higher dendrimer yield with lesser purity, this divergent method is beneficial or in other words for getting a higher yield of dendrimer purity is compromised (Najafi *et al.,* 2020).

Convergent synthesis

Jean Frechet was the first to introduce the convergent approach of dendrimer synthesis (Hawker and Frechet, 1990). This technique of production creates a dendrimer from its external-facing inwards in the direction of the core through a one to one monomers coupling thus constructing dendritic fragments increase in sizes as the synthesis proceeds (Fig. 2). Synthesis of dendrimers by convergent approach overcomes the structural defect and purity problems of divergent approach. With lesser yield overall more monodispersity, symmetric and uniform dendrimers can be created by this methodology. This method, in general, is used for the laboratory-scale synthesis of dendrimers, in other words for purity yield is compromised. For commercial-scale divergent synthesis is still favored. Most frequently used commercially existing dendrimers are PPI (Grayson and Frechet, 2001) and PAMAM (Araújo *et al.,* 2018), which are slightly structurally different owing to structural issues in every batch. But by convergent approach the dendrimer size produced has limitation owing to steric hindrance between core and dendrons going to attach with. In the divergent approach of dendrimers, this limitation of size is not an issue. Differences between both approaches are shown in Table 1.

Table 1. Comparison of the Divergent and the Convergent Approaches for the Synthesis of Dendrimers.

Advantages	Disadvantages
Divergent	
1. appropriate for dendrimers with high MW (>100 000)	1. large excess of reactant required
2. fewer reaction sequences involved	2. less control on the molecular architecture
3. large quantity production is accessible	
Convergent	
1. block copolymers are accessible	1. Limited MW of dendrimer (<100 000)
2. reaction stoichiometry is under control	2. more elaborate reaction sequences involved

Mechanism of drug delivery through dendrimers

As discussed formerly, due to many terminal functional groups and distinct 3D structures, molecules of drugs can be attached to the surface terminal groups as well as loaded in the internal voids of the dendritic polymers. Dendritic polymers can also utilize as drug carriers either by interacting with drugs at their surface functional groups via covalent or electrostatic bonds forming prodrug or encapsulating drugs within the dendritic structure.

For drug delivery there are generally two mechanisms:

First, the Initial one is by in vivo covalent bond degradation of drug dendrimer depending on the occurrence of suitable enzymes or bond cleavage environment.

Second, the other one is by variations in the physical environment and releasing of drugs such as temperature, pH. This technique is an external factor independent and takes place in receptor outer shell (exo-receptor) or core cavities (endo-receptor) (Hawker and Frechet, 1990; Palmerston *et al.,* 2017; Chauhan, 2018).

Characterization of dendrimers

Dendrimers relate both polymer chemistry because of structural repetition that is fabricated by monomers and molecular chemistry due to step by step synthetic approach used throughout their creation. Hence they

are characterized usually using analytical methods from both fields. Analytical procedures are used to examine the shape, synthesis, reaction rates, chemical composition, morphology, polydispersity, homogeneity, molecular weight, conjugation, structural purity and defects of dendrimers. They include analysis through scattering techniques, microscopic methods, electrical techniques, spectroscopic methods, chromatographic techniques and physical/rheological properties.

Spectroscopic techniques

Spectroscopic analytical techniques are centered on assessing the total radiation absorbed or produced by atomic or molecular species of interest.

These approaches have provided possibly the most extensively used instrument for the interpretation of molecular structure over and above qualitative and quantitative determination of both organic and inorganic compounds (Augustus *et al.,* 2017).

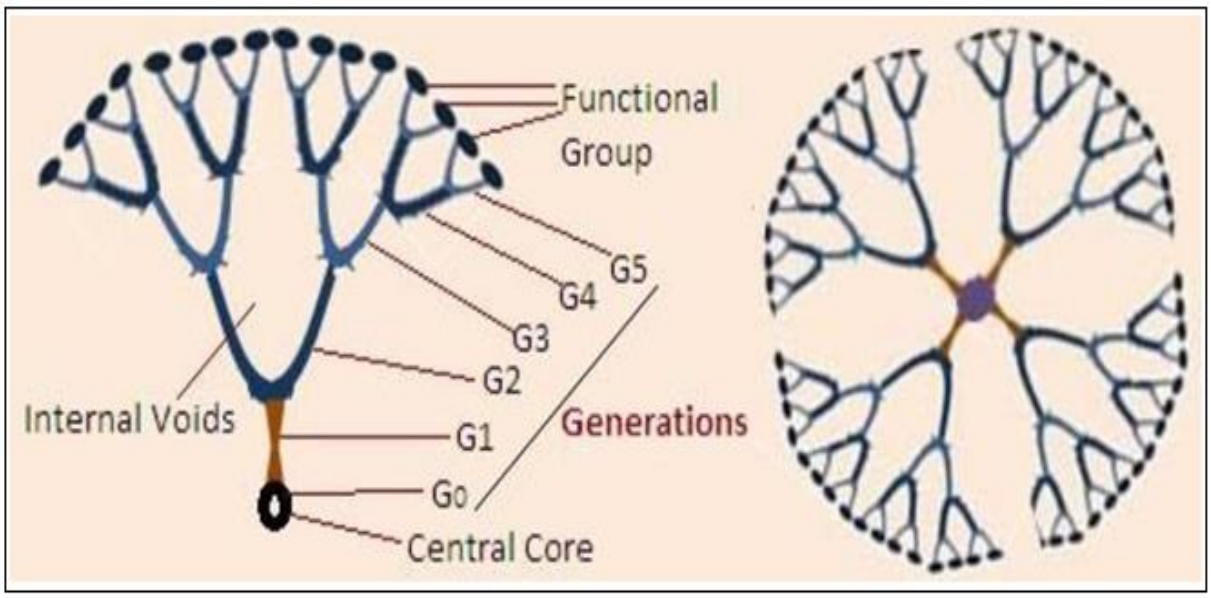

Fig. 1. Schematic representation of dendrimer structure.

Ultra Violet –Visible Spectroscopy

This method provides evidence of surface modification other than the synthesis of dendrimers due to change in lambda max value (λ) or characteristic maximum absorption. This spectroscopy is utilized to identify the functional moieties linked to dendrimers. Distinctive UV-Vis spectroscopy curves show the characteristic maximum peaks of absorption at particular wavelengths which is allotted to the impact of a conjugated moiety. Tulja investigated UV- Vis spectroscopy and its use for the categorization of dendrimer – Gold Nanocomposite material (Gautam *et al.,* 2012).

Nuclear Magnetic Resonance Spectroscopy

Nuclear Magnetic spectroscopy permits the structure determination and molecule dynamics in solution (Augustus *et al.,* 2017). Victoria used one and two-dimensional NMR studies to probe the melamine dendrimer confirmation of which bears NMR unique signals from the centre to the boundary (Mekuria *et al.,* 2017).

Raman Spectroscopy

The method used to study vibration, low-frequency and rotational forms in a system. Furer applied the Raman Spectroscopy technique in the characterization of phosphorus and polypropylene Imine (PPI) dendrimers and study of cyclodehydration of polyphenylene dendrimers (Kim *et al.,* 2016).

Microscopic Techniques

Scanning Electron Microscopy (SEM): Study of dendrimer surface topography is usually determined

by applying SEM. For a deeper understanding of the surface properties, Dadapeer applied SEM in the study of phenyl-OH terminated dendrimer (Dadapeer *et al.,* 2010).

Electron Paramagnetic Resonance (EPR)

EPR is useful for studying chemical species having one or more unpaired electrons for example inorganic complexes retaining transition metal ions or inorganic and organic free radicals. Ottaviani *et al.* stated the use of EPR in the investigation of the dendrimer adsorption on zeolite, homoporous silica and activated alumina and is magnified on an imaging device (Kontogiannopoulos *et al.,* 2018).

Electrophoresis: This procedure delivers useful data about the homogeneity and purity of numerous categories of water-soluble dendrimers. Ottaviani *et al.* examined the purity of PAMAM dendrimers with the use of ^{13}C NMR spectroscopy, gel electrophoresis and mass spectrometry (Yu *et al.,* 2017).

Thermo Gravimetric Analysis (TGA)

TGA measures change in weight regarding the change in sample temperature. Correspondingly, DTA (Differential Thermal Analysis) notify if the material changes were endothermic or exothermic. Thus TGA-DTA measures weight changes and heat flow in a controlled atmosphere in a sample concerning temperature. Dadapeer *et al.* considered the TGA of phosphorus comprising dendrimer with a core unit of diphenylsilanediol. As for temperature change, the changes in weight and thermal stability of dendritic molecules were measured by TGA-DTA (Dadapeer *et al.,* 2010).

Dendrimers and their Applications as Novel Drug Delivery Carriers

The study of interactions among solid surfaces and dendrimers provides precise information that can magnify the options of consuming dendrimers as novel adsorbents on solids. To produce composite materials, solid surface properties are modified by using dendrimers that may be compatible with changing environments thus, improving the application range of dendrimer–surface supramolecular systems (Augustus *et al.,* 2017). Dendrimers are produced by sequences of repetitive stages. The repetitive progression of branching was first described by Vogtle. This was followed by Tomalia for the development of the independent divergent macromolecular synthesis of “true dendrimers". (Tomalia *et al.*,1984; Tomalia *et al.,* 1985). For these macromolecules, they were the earliest to form coin the term dendrimer and to define the production of poly (amidoamine) (PAMAM) dendrimer comprehensively.

Then Frechet introduced a convergent synthetic method of dendrimer synthesis (Hawker and Frechet, 1990). Dendrimers direct a design including periphery and interior chemical modifications because of the solvent approachability in dendrimer voids. For adsorption studies, rigid dendrimers are suitable models as they remain solid at a wide temperature range (Ottaviani *et al.,* 2003).

In current times the researchers have been interested in free dendrimers while the applications and properties of supported dendrimers (functionalized dendrimers) are hardly reported. Dendrimers are highly branched having special characteristics like different terminal functional groups, lesser viscosity and higher density. Owing to these distinctive features it offers multiple applications in particular as solubility enhancer, drug delivery, dendritic nanomaterials, dendrimer-based nanomedicine, light-harvesting, drug delivery carriers, light-emitting diodes liquid crystals membrane separation and chemical modification (Gupta *et al.,* 2006; Gupta and Nayak, 2015).

Considering the point that the surface, interior and core of dendrimer molecules can be polyfunctionalized to enhance several applications. Around fifty families of dendrimers with distinctive properties have been established. Their unmatched consistency of molecules, internal unique cavities and polyfunctional surface make dendrimer molecules appropriate for a wide range of uses (Klajnert *et al.,*

2001; Sánchez *et al.,* 2019).

Biomedical

Dendrimer functionalization creates the opportunity for control over size, shape, density, branching, surface functionality and architectural design. The particulate system with definite shapes and sizes is of prominence in medical applications for instance drug delivery (Klajnert *et al.,* 2001; Santos *et al.,* 2020). Dendrimers are appropriate vehicles with the potential to attach with multiple groups, size, easy preparation and functionalization for ophthalmic drug delivery (Augustus *et al.,* 2017).

Nanotechnology

Organic electronic devices such as organic solar cells, organic optical detectors and organic thin-film transistors are designated as branched or linear dendrimers incorporating an exact component that acts as hole-transporting, hole-blocking materials, or hole-injecting (Vandamme and Brobeck, 2005). Nanostructure features of dendrimers have attracted attention. Insoluble materials like metals can be encapsulated in dendrimers by their transportation to the interior through a solvent (Augustus *et al.,* 2017). The use of fluorinated dendrimer compounds was reported by Cooper for the extraction of strong hydrophilic compounds into liquefied CO from water (Mizugaki *et al.,* 1999; Ulku and Burcu, 2020). In a similar manner X, Shi accounted for the manipulation, synthesis and characterization of Iron Sulfide dendrimer - stabilized nanoparticle that is highly energetic in the reductive dechlorination of chlorinated hydrocarbons (Shahbazi *et al.,* 2013).

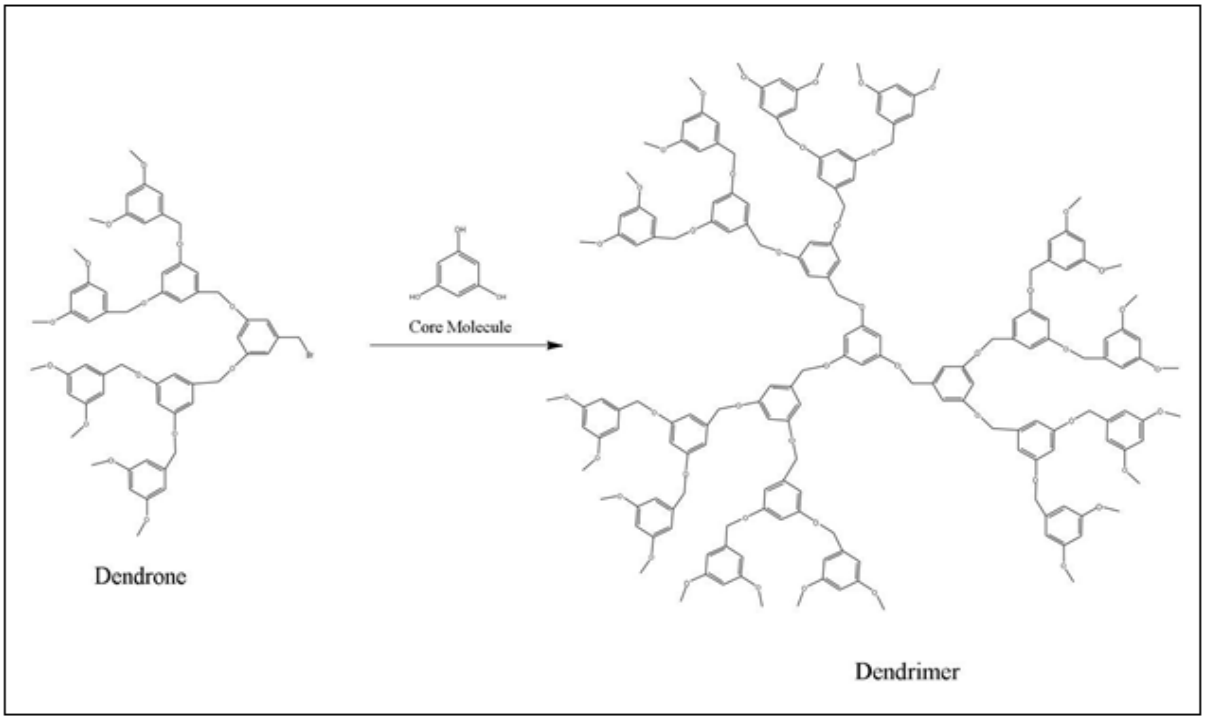

Fig. 2. The convergent approach of dendrimer synthesis.

Catalyst

Dendrimers have been utilized as catalysts in large quantum as they have various active target sites that assemble as intermediates between heterogeneous and homogeneous catalysts. This also allows encapsulation of a single catalytic site whose action can be improved by the superstructure of dendrimers (Ye *at al.,* 2017.

Solubility enhancers: Various ingredients are having a strong therapeutic activity but for therapeutic purposes, they haven't been utilized owing to lack of solubility in suitable pharmaceutical solvents. Water-soluble dendrimers have the capability of solubilizing and binding small hydrophobic acidic molecules with antibacterial or antifungal properties. Dendrimers have been named unimolecular micelles with a

hydrophilic surface and hydrophobic core (Sorroza-Martínez *et al.,* 2020).

Dendrimers do not consume a CMC or critical micelle concentration, contrary to traditional micelles. This specific character offers the chances of solubility of poorly soluble drugs by encapsulation inside the structure of dendrimers at almost all concentrations of dendrimers. A hydrophobic-hydrophilic core-shell dendrimer molecule with long-chain alkane exterior and Poly (Amidoamine) interior was exposed to fix 5-flurouracil, an anti-tumor water-soluble drug (Gillies and Frechet, 2005). Subsequently, on coating, the dendrimer–fatty acid macromolecule with a phospholipid, bioavailability of 5-flurouracil orally in rats was almost twofold of the magnitude of free 5-flurouracil. Carriers based on dendrimer could provide the slot to boost the bioavailability of orally challenging drug Propranolol, the solubility of propranolol increased by over twice of level on conjugation with surface-modified G3 PAMAM dendrimer. Therefore, dendrimeric nanocarriers extend the potential to improve the drug bioavailability that is substrates for efflux transporters and poorly soluble (Najlah and D'Emanuele, 2006).

Dendrimers as imaging agents

Contrast macromolecular agents have developed very significant tools in diagnostic modern medicine. An early dendrimer application to imaging tools was revealed in the US patent. The patent unfolds the novel stable complex agent for radionucleotide-derivative phosphonate dendrimer imaging the mammal's skeletal system. Multiple binding sites are provided by dendrimers on the periphery, permitting many MRI (magnetic resonance imaging) contrasting agent facilities to affix to them. One molecule of dendrimer can host up to 24 contrast complexing agents (depends on generation), in this manner achieving a higher signal-to-noise ratio (Esmaeili *et al.,* 2019). Dendrimers for oral delivery of drugs with diameters ranging from 2.5 to 6 nm appeared to approach the ideal progress to smaller systems. The problem of aggregation and flocculation of the *in vivo* system, oral dendrimer uptakes are not enhanced as accepted. Using polyoxyethylene ionic groups or glycol chains can diminish this problem, but oral uptake of the surface dendrimers is then inhibited by the hydrophilic nature. Drug-dendrimer size, surface charge, molecular weight, the concentration of active molecule and incubation time impart diverse characteristics for oral dendrimer delivery. Generally, cationic dendrimer compounds are extra toxic and disrupt the tight junctions. With the increase in net surface area and generation, the effects of dendrimers increased. Dendrimer surface modification by carboxylic groups significantly diminished the toxicity, while tight junctions are still opened by modified dendrimers. In our view, it's a matter of period before numerous dendrimers application for CNS drug delivery of therapeutic and diagnostic agents (Zahang *et al.,* 2018).

Anticancer drug delivery

Intended for many anticancer drug deliveries, one of the chief applications of dendrimers is to act as a delivery vehicle for delivery. The structure and dendrimer surface tunable functionality permits for the conjugation/ encapsulation of multiple moieties, either on the surface or inside the core, interpreting those perfect carriers for anticancer drug delivery. Frequent dendrimer examples are mediating the targeted delivery of drugs. Jesus in 2002 had discovered the option of 2, 2-bis (hydroxymethyl) propanoic acid created a dendritic scaffold for doxorubicin in-vivo and in-vitro as a drug delivery carrier (Padilla De Jesús *et al.,* 2002). Many researchers have also discovered the probability of incorporating cisplatin in dendrimers.

An early example is PAMAM dendritic generation 3.5 conjugated through the sodium carboxylate surface to cisplatin giving a dendrimer–platinate (dendrimer–Pt; 20–25 wt% platinum), resulting in a nanoformulation properly water-soluble with the capability to release in-vitro cisplatin slowly. By applying this system, they fruitfully created dendrimers from 0.5 to 5.5 generations. Additionally, on reaction with 1 bromoacetyl-5-fluorouracil,

dendrimer forms dendrimer–5FU conjugates (Wu *et al.,* 2020). PEG-dendrimers are one sub-class of dendrimers that invite various scientists due to their toxicity low level, comparatively lesser accumulation in different body organs and prolonged circulation time in blood. Similarly, in-vivo experimentations show a considerably greater accumulation in the tissues of the tumor due to the EPR (enhanced permeability and retention) effect. PEGylated dendrimers are in general produced by the conjugation of polyethylene oxide (PEO) or PEG chains to a polyfunctional dendritic chain. Furthermore, PEG-PAMAM dendrimers were used for the 5FU incorporation. Therefore, as estimated, it was perceived that this creation is appropriate for prolonged anticancer drug delivery without producing any major hematological disorders by blood-level and in vitro readings in albino rats. PEGylation also contributed further advantage to the formulation of dendrimer by reducing hemolytic toxicity and drug leakage. This, consecutively, could expand the capacity of drug-loading and stabilize corresponding systems in the body (Entezar-Almahdi *et al.,* 2020).

Dendritic micelles Dendrimers

The monodisperse, highly branched macromolecules have a huge quantity of surface groups that are tunable and an internal that offers microenvironment as well as space appropriate for guest-host chemistry. Generally, dendritic micelles are unimolecular and do not undergo the low CMC even that the micelles based on linear polymer have. Likewise, they have been presented to be internalized rapidly into cells due to their dimensions in the nanometer scale through endocytosis (Parshad *et al.,* 2019). Due to these distinctive features, dendritic micelles are being freshly studied for uses as drug carriers, in gene therapy and as imaging contrast agents. From the discussion above it is evident that dendrimers with PEG or anionic groups on the boundary are favorable for drug delivery carriers. Additionally, biocompatible functionalized dendrimers will be striking for multiple drug-dendrimer conjugates. It will be exciting to have dendrimers that are highly functionalized, moreover, functionalities are directed towards the concave interior of the dendritic micelles for better drug encapsulation (Wang *et al.,* 2019).

Dendrimer-based nanoparticles for lung delivery

The PAMAM dendrimers' ability to augment in-vivo plasmid-DNA gene transfer and evaluated the lung targeting by alternative administration routes. The efficacy and safety of the dendrimer-drug formulations inhibit deep vein thrombosis, both *in situ* and *in vivo*. They investigated that cationic dendrimers can be utilized as pulmonary drug delivery carriers for anionic drug molecules, having large molecular weight. These delivery carriers bind anionic drugs via electrostatic interactions most likely and through neutralization of charge increase absorption of the drug (Gorain *et al.,* 2019).

Dendritic catalysts/enzymes

The combination of high solubility and high surface area make dendrimers valuable as nanoscale catalysts. Dendrimers have a polyfunctional surface and almost all catalytic positions are constantly exposed to the reaction mixture. Ultrafiltration methods are used to recover them from the reaction mixture. Yet to create a microenvironment, the dendritic shells can be utilized as promising candidates for catalysis and provision of shielding effect to the functional groups at the dendrimer core. Owing to 'pseudo'-spherical nature and their resulting conformation, the metal resides in these dendritic catalysts, available for substrate reagents and molecules, displaying a characteristic solubility, specificity and swift kinetics. The catalysis of metallo dendritic catalysts with (metallo) dendrimers comprising chiral ligands, catalysis with phosphine-based dendrimers, and non-metal comprising dendrimers are approximate examples of dendritic enzymes and catalysts (Gao *et al.,* 2017).

Biocompatibility of dendrimers

In nanomedicine, the most significant feature necessary for the extensive use of dendritic polymers is their non-immunogenic property, low toxicity and appropriate excretory pathways. To date, primarily *in vitro* data for dendrimer cytotoxicity has been seen,

while limited mammalian in vivo studies on rats or mice is also executed (Cui *et al.,* 2018). Though, clinically advanced human trials are currently undertaken with topical application of VivaGel R (i.e. anionic surface-functionalized polylysine dendrimer) having utility in the prevention of genital herpes and HIV. However, the surface functionality of the dendrimer in combination with the size i.e. generation level brings in toxicity (Kandi *et al.,* 2019).

Conclusion

The massive architecture control over the dendritic compounds, their properties like shape, size, density, branch length and surface functionality isolate them as ideal carriers for biomedical use. The application in gene transfection, drug delivery and imaging is a way forward. Besides having seen decades of work in synthesis and application, the multi-step process still demands attention. The breakthrough with dendrimer promises a new era of dosage form until then a very few cost-effective applications shall be attained.

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