INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

Review Article

A Review about Dendrimers: Synthesis, Types, Characterization and Applications

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Abstract

This review provides brief information concerning with the dendrimer, its synthesis, characterization and application in drug delivery. Dendrimer consist of well defined size, shape, molecular weight and monodispersity. These properties formulate the dendrimers a suitable carrier in drug delivery application. Dendrimer are built from number of molecular entities of colloidal paticles that exists in equilibrium with the molecules or ions in nature and due to this increases the solubility of poorly soluble drugs. Due to their distinct structural design these have improved physical and chemical properties. The compatibility between DNA, heparin and polyanions make them more versatile. Self assembly of molecules produces a quicker means of producing nanoscopic functional and structural systems. But the genuine effectiveness in drug delivery can be assessed only after accepting their behavior in vivo. Studies have explored the biological possiblities of dendrimers such as to transportation of genes, development of vaccines, antiviral, antibacterial and anticancer therapies. This review also describes how the dendrimer interrelate with numerous drugs and the prospective of these macromolecules in addition with the drug nanocarriers in transdermal route of administration, ocular, respiratory, oral and intravenous administration. Dendrimers assure superior prospect protrusion for the biomedicine. This review provides a brief discussion of dendrimers' physico-chemical properties and their potential use in a range of areas of research, technology and treatment.

Keywords: Dendrimer, Synthesis, Application, Properties.

INTRODUCTION

Dendrimers are extremely branched, globular, multivalent, monodisperse molecules with synthetic elasticity and many possible applications ranging from catalysis to electronics and drug release. Dendrimers and dendritic molecules are the subject of significant educational and industrial interest [1]. Dendrimers are repetitively branched molecules [2]. The name come from the Greek word "δένδρον" (diverse dendron), which interpret to "tree". Identical terms for dendrimer contain arborols and cascade molecules. However, Dendrimer is presently the internationally established term. A dendrimer is classically symmetric around the core, and often adopt a globular three-dimensional morphology. The word dendron is also encounter regularly. The differentiation between dendrons and dendrimers is well explained in figure 1(A&B), but the terms are classically encounter interchangeably [3]. Go, G1, G2 G3 and G4 designated as zero generation to four generation respectively (Figure1A).

HISTORY OF DENDRIMER

Dendrimers are an attractive exclusive class of polymers with controlled structure. A dendrimer is both a covalently assemble molecule and also a distinct nanoparticle. The first dendrimers be completed by divergent synthesis advanced by Fritz Vogtle in 1978, [4] R.G. Denkewalter at Allied

Corporation in 1981, [5] Donald Tomalia at Dow Chemical in 1983 and in 1985, [9] and by George Newkome in 1985 [6]. In 1990 a convergent synthetic approach was introduce by Jean Fréchet [7]. A lot of research has already been completed by studying the different properties and application of dendrimers but a lot of researchers still believe it to be in its initial stages.

SYNTHESIS:

General Methods of Dendrimer Synthesis:

Dendrimers can consider three major parts i.e. a core, an inner shell, and an outer shell. A dendrimer can be generating by varying functionality in each of this portion to categorize properties such as solubility, thermal stability, and addition of compounds for meticulous application [8]. Synthetic procedure can also correctly manage the size and number of branches on the dendrimer. There are two different methods of dendrimer synthesis, divergent synthesis and convergent synthesis [9].

Divergent Method:

The dendrimer is assembling to from a multifunctional core, which is extended outward by a sequence of reactions, commonly a Michael addition reaction. Each step of the reaction must be determined to full completion to prevent mistakes in the dendrimer, which can grounds trailing generations (some branches are shorter than the others). Such impurities can collision the functionality and symmetry of the dendrimer, but are tremendously difficult to purify out because the relative size variation between perfect and imperfect dendrimers is very small. The major disadvantage of this approach is that the incomplete growth and the side reactions lead to imperfect dendrimers. To minimize these side reactions and imperfections, it's recommended to use a large excess of reagents. The divergent growth reaction of dendrimer can be shown in

Convergent Method:

Dendrimers are constructed from beginning of small molecules that end up at the surface of the sphere, and reactions precede inmost building inward and are eventually attached to a core. This method makes it very much easier to eliminate impurities and shorter twigs along the way, so that the final dendrimer is more mono-disperse. However dendrimers ended this way are not as large as those made by divergent methods because crowding due to stearic property along the core is restrictive [10]. The convergent growth reaction of dendrimer can show in figure 3.

Main problem of convergent method is that we cannot manufacture a large molecule for drug loading due to crowding and stearic effect [10].

Click chemistry:

Dendrimers have been prepared via click chemistry, employing Diels-Alder reactions,[26] thiol-yne reactions and azide-alkyne reactions [11]. Click chemistry was first introduced by K. Barry Sharoless of the Scripps Research Institute in 2001 and describe chemistry modified to engender substances rapidly and consistent by combination of small units collectively. It is not a solitary reaction, but was intended to imitate nature, that can also generate molecules by joining small modular units [12].

An attractive Click chemistry reaction would- (a) a modular (b) wide in scope (c) provide very high chemical yields (d) produce only harmless byproducts (e) be stereospecific (g) physicologically stable (h) shows a huge thermodynamic driving force (>84 kJ/mol) to errand a reaction through a single reaction product (i) contain elevated atom economy. A separate exothermic reaction makes a reactant "spring-loaded" [11].

Factors affecting dendrimers synthesis:

There are different factors which can affect dendrimer synthesis. The non-ideal dendrimer expansion may be manifested through a variety of ways which includes:

1. Incomplete addition reaction.
2. Intermolecular cyclization.
3. Fragmentation.
4. Solvolysis of terminal functionalities.

Classification of dendrimer: Dendrimer can be classification on the basis of their shape, structure, branching, solubility, chirality and attachment, which can be classified in table 1.

Properties of Dendrimers:

Tentatively, dendrimers are mono-dispersive. Due to small imperfection during the mechanized process, the polydispersity index is about 1.001. Polydispersity of 1.0007 for PAMAM has been report. Opposing to linear polymers, the viscosity will reached with the maximum value that starts to decline [14].

The decline in viscosity is a result of prohibiting the interaction with the outer branches between molecules at a higher generation. The glass transition temperature (Tg) of dendrimers which follows similar trends. It reaches to a maximum Tg and levels off at superior molecular weights [15]. This behavior is the outcome of absence in embarrassment at higher

molecular weights. Dendrimers differ from classical random coil molecules in that they are vastly branched, three-dimensional macromolecules with a branch point at each monomer unit. Several properties of dendrimer are listed below in the given table no.2.

Types of dendrimer: Dendrimer can be differentiated on the basis of their shape, end functional groups and internal cavities, which can be classified in table 3.

Method for characterization of dendritic polymer:
Characterizations of dendrimer by various methods, which are listed below in table 4.

Application of dendrimer:
Dendrimer hold its unique structural characteristics like nanoscopic size, spheroidal surface, high branching, cavernous interior, etc. and exciting properties, like low viscosity, high solubility, high reactivity, in arrangement with the high functionalities of the dendritic polymers optional that they have broad number of prospective applications in different fields [48]. These integrated medicinal and diagnosis applications includes gene therapy and chemical sensors drug delivery system, adhesive and coatings, light harvesting material, catalyst, electronic applications, separating agents, and many other [49, 50].

Dendrimers in biomedical field:
The dendritic polymer had benefit in biomedical applications. These dendritic polymers are similar to protein, enzymes and viruses and easily functionalized. Dendrimers and other molecules can also be attached to periphery or can be encapsulated in their interior voids. The dendrimer should have certain merits for its efficacy as biological agents. PAMAM dendrimers can also be used to target tumor cells. Targeting groups can be conjugated to the host dendrimers surface[51] to allow the imaging agent to bond selectively to specific site such as receptors on tumour cell to progress recognition. Cisplatin was complex to the exterior groups of a carboxylate-terminated PAMAM dendrimer which leads to a tenfold enhance in the solubility of cisplatin compare to the free drug [69].

Dendrimer as magnetic resonance imaging contrast agents:
Dendrimer based metal chelates lead as a magnetic resonance imaging contrasting agents. Dendrimers are tremendously suited and are used as image differentiating media because of their vast properties. Many tests are carried on dendrimers which have exposed that dendrimers are stronger contrast agent than conservational ones. Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged improvement with a half-life of 200 min compared to 24 min for monovalent gadolinium agent. This prolonged augmented time is tremendously useful for 3D time-of-flight MR angiography [52].

Dendrimers in Antitumor Therapy:
Dendrimers molecule were used as diagnostic reagent for tumour identifying by magnetic resonance imaging and as contrast agent; by varying the size and hydrophilicity and by combined with tumour targeting antibodies, these compounds can be used as specific imaging purpose[53] The drug should be non-toxic, under no irradiative environment, thus act as prodrug when not irradiated. Dendrimers contain photosensitises named 5- aminolevulinic acid has been attach to the surface of dendrimers and studied as an agent for photodynamic therapy (PDT) of tumorigenic keratinocytes [54]. The therapeutic uses of dendrimers within the cancer field where several examples of targeting tumours for diagnostic purpose have been described and where it was possible to describe a cancer specific cell surface module that can be embattled.

Dendrimers as Gene Transfer Reagents:
Gene transfection is a straight forward approach where DNA is attached to a nanoparticle of inert solid, which is then openly targeted to the cell nucleus. As transfection, if eukaryotic cells is a method for effectual changes in the genetic material of cells [55]. The use of dendrimers for transfection was primary reported by the group of Szoka and Baker [56]. PAMAM dendrimers were the first establish to be helpful for transfection. The company named Quiagen developed a industrial transfection arrangement based on PAMAM dendrimers followed by the work of Szoda et al and Baker et al [57]. Dendrimers are actively under inspection for the delivery of DNA and organic molecule drugs, chiefly for cancer therapy. The amino ended PAMAM or PPI dendrimers as non-viral gene transfer agents, providing the transfection of DNA by endocytosis into the cell nucleus [58, 59]. Furthermore, a chain of amphiphilic dendrimer based on the stiff diphenylethyne core was manufactured and their actions as transfection agent were identified [60]. In this study, dendritic amidoamine side chains of different generations were covalently connect to the chitosan which was selected to merge the biological actions of chitosan in gene delivery, antibacterial activity and lesion healing activity with the delivery profit establish for dendrimers.

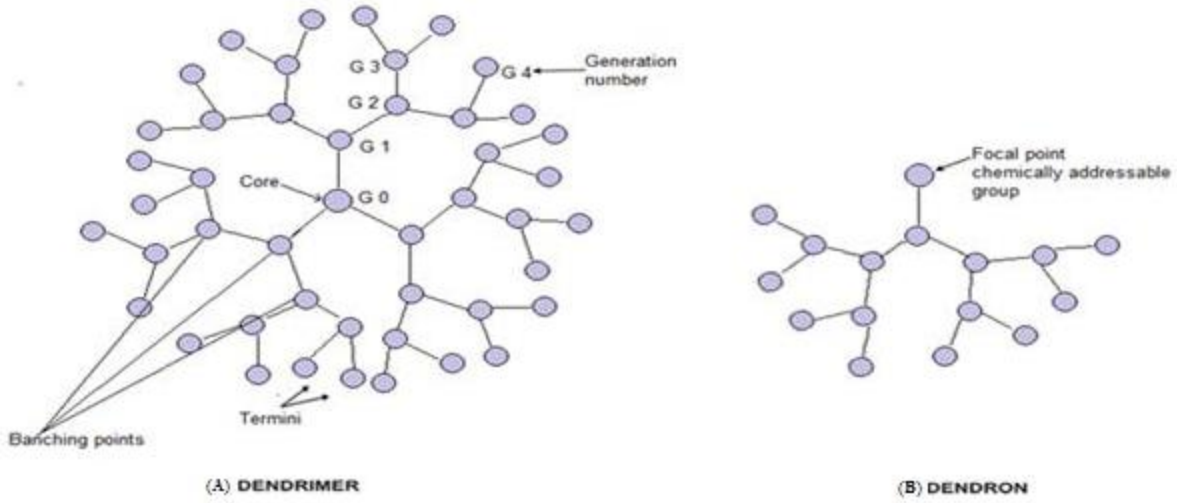

Figure1
(A) Structure of dendrimer with different generation (G-0 to G4) & (B) structure of Dendron

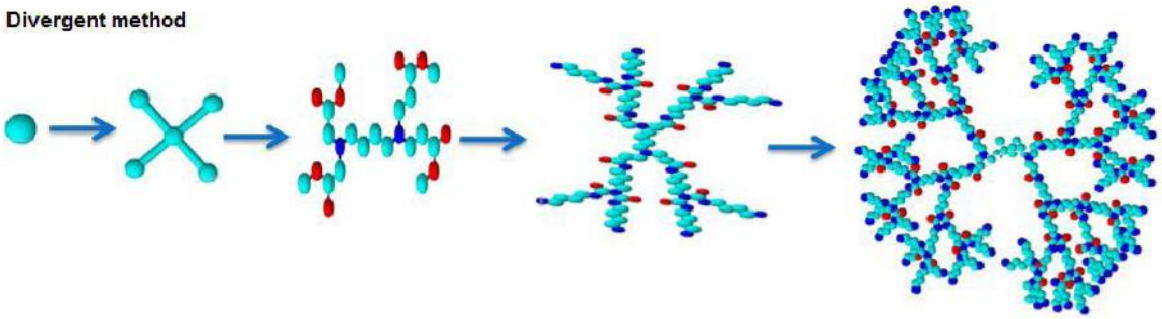

Figure 2
Divergent method of dendrimer synthesis.

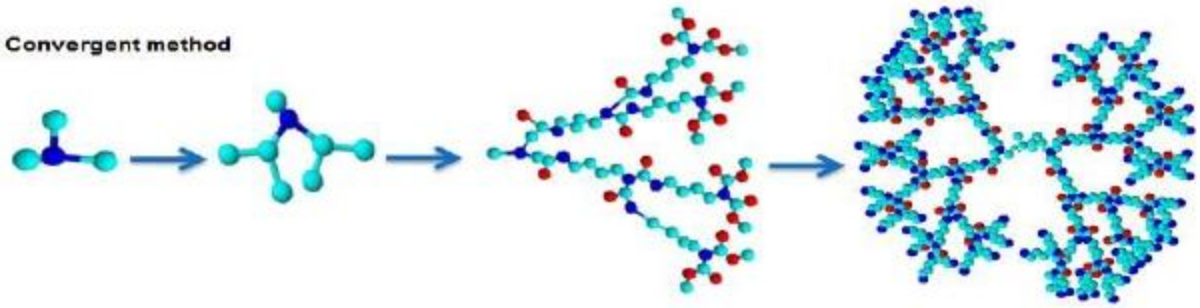

Figure 3
Convergent method of dendrimer synthesis.

Table 1
Classification of Dendrimers

S.No.	Classification of dendrimer	Application/Methods
1.	Simple Dendrimer	They have simple monomer units. The convergent synthesis of a sequence of monodisperse are lester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 and 46 benzene rings linked symmetrically and have molecular diameters of 45 A [13].
2.	Liquid crystalline dendrimer	These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer. Functionalization to the end group of carbosilane dendrimers with 36 mesogenic units which can be attached through a C-5 spacer, and leads to liquid crystalline dendrimers that form broad smectic phase in the temperature range of 17°C to 130°C [13].
3.	Chiral dendrimer	In chiral dendrimers the chirality is based on the building of 4 constitutionall y assorted but chemically alike branches to an achiral core e.g. chiral dendrimers obatined from pentaerythritol [13].
4.	Micellar dendrimer	These are unimolecular micelle arrangement dendrimers. Fully aromatic, water-soluble dendrimers forming a collection of aromatic polymeric chain which able to generate an environment that resembles some micellar structures, which forms complex with small organic molecules in water [13].
5.	Hybrid dendrimers	These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. Which provide an opening to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers [13].
6.	Amplhiphilic dendrimer	These are the class of globular dendrimers that have asymmetrical but highly controlled division of chain end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion [13].
7.	Metallo dendrimer	Dendrimers attached with the metal ion to form the complexation either in the interior or on the peripheral, which may be regarded as metallodendrimers. The ruthenium bipyridine complex based dendrimer have attribute electrochemical and luminescence properties [13].

Table 2
Properties of Dendrimer[16]

S.No.	Properties	Dendrimer
1	Structure	Compact and Globular
2	Shape	Spherical
3	Architecture	Regular
4	Structural control	Very high
5	Synthesis	Stepwise growth
6	Crystallanity	Non-crystalline and amorphous materials Lower glass temperatures
7	Reactivity	High
8	Aqueous solubility	High
9	Nonpolar solubility	High
10	Viscosity	Non linear relationship with molecular weight
11	Ionic conductivity	High
12	Compressibility	Low
13	Polydispersity	Monodi sperse

Dendrimers in targeted drug delivery:
Targeted drug delivery is a method of introducing medicine to a patient in a way that increases the attentiveness of medication in meticulous part of body. Dendrimers have multifunctionality and high possibilities for drug delivery applications as they have high density and wide range of functional groups on its surface. Due to the twice functional group, the plasma level of the drugs will persist at desired level for longer phase of time and increase its Pharmaceutical effectiveness. Generally, the therapeutic effectiveness of drug is diminished due to low bioavailability, insolubility, toxicity and the decomposition of drug under biological circumstances [50]. Using Dendrimers, targeting moieties against conjugated drug molecule, the above shortcomings can be overcome.

Dendrimers in drug delivery:
Drug molecule can be loaded in the centre and also to

the surface of dendrimers. Encapsulations of the well-known anticancer drug cisplatin within PAMAM dendrimer provide conjugates which can slow down the release and provide higher accumulation in solid tumours and decrease toxicity than free cisplatin [61]. The encapsulation of silver salts with PAMAM dendrimers produce conjugates that can reveal slow silver release rates along with antimicrobial activities against different gram positive bacteria [62,63]. Dendrimers are highly soluble, due to which, solubility of drug in body can be increased. Drug molecules can be induced into dendrimers through complexation or encapsulation [64]. Therapeutic agents can be attached to a dendrimer for the delivery of drugs. For example, dendrimers in Boron Neutron Capture Therapy (BNCT) Vol.48 Dendrimers 2005.

Dendrimer in transdermal drug delivery:

Transdermal drug delivery had approached into existence long back. To progress the effectiveness of the drug, transdermal drug delivery system was applied. Drug delivery through skin to attain a systematic effect of drug is known as transdermal drug delivery. Transdermal delivery provide controlled, steady administration of the drug which extends the action of drug having short half life during the reservoir of drug available in the delivery system and its controlled release description [65] which are very efficient in treatment of acute and chronic rheumatoid and osteoarthritis, could be recovering the drug penetration through the skin as diffusion enhancers [66].

Dendrimers in oral drug delivery:

Oral drug delivery is the most favorable and has arriving more attention in the pharmaceutical field because of broadmindedness of production, low cost, expediency of easiness of administration and suppleness in formulation of dosage form. The controlled release method for the oral use are mainly solids and based on dissolution, diffusion or a mixture of both mechanisms in the control of release rate of drug [65]. One significant advantage of oral drug delivery is less fluctuating plasma drug level is maintained with controlled drug delivery systems, because the drug is gradually released from the dosage continuously and maintains the stable blood level. Along with the advantages there are some disadvantages of oral delivery route i.e. low solubility in aqueous solutions and low diffusion across intestinal membranes [67]. D'Emanuele and his researcher investigated that the result of dendrimer generation and conjugation on the cytotoxicity, penetration and transfer mechanism of PAMAM dendrimer [68]. As the concentration and generation increased, the increase in cytotoxicity and penetration of dendrimers resulted. While reducing in cytotoxicity was experienced by conjugation with lauryl chloride.

Dendrimers in ocular drug delivery:

The topical application of active drugs to the eye is the most approved route of administration for the management of various ocular disorders. Dendrimers offer unique solutions to complex delivery problems for ocular drug delivery. A supreme ocular drug delivery system must be non-irritating, biocompatible, sterile, isotonic and biodegradable [69]. The recent trouble for ocular drug delivery focus on rising the residence time of pilocarpine in the eye was conquer by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface modified dendrimers were optimised to enhance pilocarpine bioavailability [70]. Dendrimer show physiochemical properties like pH, osmolality, and viscosity etc that shows some additional compatible with ocular dosage form to devise dissimilar formulations for ocular infection. The important compensation of dendrimer in ocular drug delivery is perseverance in corneal residence time, which can provide better bioavailability of drug, and initiate in the form of eye drops. Dendrimers facilitate in achieving improved bioavailability, sustained, controlled as well as targeted release of drug [71].

Dendrimers in pulmonary drug delivery:

Dendrimers had been reported for pulmonary drug delivery in these studies, by measuring plasma anti-factor Xa activity using PAMAM dendrimers was enhancing the pulmonary absorption of Enoxaparin, and by observing avoidance efficacy of deep vein thrombosis in a rodent model, it was experienced that G2 and G3 generation optimistically charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40% while G2.5 PAMAM half generation dendrimers contains negatively charged carboxylic groups had no effect. So that positively charged dendrimers are appropriate carrier for Enoxaparin pulmonary delivery [72].

Dendrimers used for enhancing the solubility:

PAMAM dendrimers are conventional to have potential applications in escalating the solubility for drug delivery systems [73]. Dendrimers had hydrophilic exterior and hydrophilic interiors that are conscientious for its unimolecular micelle nature, which are responsible for its solubilisation performance [74]. Dendrimer have unimolecular micelle and do not possess a critical micelle concentration. These properties provide the

opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure [75]. Dendrimer base carriers propose the chance to improve the oral bioavailability of problematical drugs. Thus, dendrimer nano-carriers recommend the possible ways to recover the bioavailability of drugs which are dimly soluble and/or substrates for efflux transporters.

Table 3
Types of Dendrimers

S.No.	Types of dendrimer	Synthesis	Examples	Identification
1.	PAMAM (Poly Amido Amine) Dendrimer	Divergent	Dendritech ™ (USA)	These are spheroidal or ellipsoidal in shape.[17] It has high solubility and reactivity due to incidence of a number of functional end groups and empty internal cavities [18-19].
2.	PPI (Poly Propylene Imine) Dendrimer	Divergent	Asramol by DSM (Netherlands)	Its core structure is based on Di amino butane with primary amines as end groups and tertiary propylene amines as center. These are commercially available up to G-5 and are extensively used in material science and biology [20].
3.	Chiral Dendrimer	Convergent	chiral dendrimers derived from pentaerythritol	The chirality of the dendrimers was based upon the building of constitutionally different but chemically alike branches to chiral core [21].
4.	Multilingual Dendrimers	Convergent	VivaGel	These are the dendrimers which hold multiple copies of a particular functional group on their surface [22].
5.	Tecto Dendrimers	Divergent	Stratus® CS Acute Care ™, Starburst®, Mercapto	These were made up of core dendrimers, which can be surrounded by other dendrimers, which execute a specific function leading to a smart therapeutic system used for diagnose the diseased state and deliver API to the accepted diseased cell [22].
6.	Hybrid Dendrimers	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes	These dendrimers have characteristic of both dendritic and linear polymer [22].
7.	Amphiphilic Dendrimers	Divergent	SuperFect, Hydraamphiphiles and bola-amphiphiles	These have one half that is electron donating and another half is electron retreating.
8.	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 delivery [23].
9.	Frechet-Type Dendrimers	Convergent	Frechet type dendron azides, TM Priostar	These were based on polybenzyl ether hyper branched skeleton. Carboxylic acid group attached on the surface of dendrimers that provides site for further functionalization and also improve the solubility of dendrimers [23].
10.	PAMAMOS (Poly Amidoamine Organosilicon) Dendrimers	Convergent and Divergent	SARSOX	These are silicon containing commercial dendrimers which are inverted unimolecular micelles and contains exterior hydrophobic organosilicon (OS) and interiorly hydrophilic, nucleophilic polyamidoamine [23].
11	Multiple Antigen Peptide Dendrimers	Convergent and Divergent	vaccine and diagnostic research	These are dendron-like molecular assembly based upon a polylysine frame. Lysine with its alkyl amino side-chain performed as a excellent monomer for the overture of frequent branching points [24].

Table 4
characterization of dendritic polymer

A	**Spectroscopy and spectrometry methods**	**Spectroscopy and spectrometry methods of characterization of dendritic polymer are as follows** [25-30].
	Ultra-violet-visible spectroscopy (UV-VIS)	Provides information for monitoring the synthesis of dendrimers. The intensity of the absorption band is basically proportional to the number of chromophoric units.
	Infra red spectroscopy (IR)	Provides information for routine analysis of the chemical transformations going at the surface of dendrimers.
	Near infra red spectroscopy	Provides information for the characterization of delocalize π-π stacking interaction between end groups of modified PAMAM.
	Fluorescence	Provides information for increasingly high Sensitivity of fluorescence used to quantify defects during the synthesis of dendrimers.
	Mass spectroscopy	Chemical ionization or fast atom bombardment used for the characterization of small dendrimers whose mass is below 3000 Da. Electrospray ionization used for dendrimers which are able to form stable multicharged species.
	X-ray diffraction (XRD)	Provides information to allow precise determination of the chemical composition, structure, size and shape of Dendrimer.
B	**Scattering techniques**	Scattering techniques for characterization of dendritic polymer are as follows [31-34].
	Small angle X-ray scattering (SAXS)	Provides information about their average radius of gyration (Rg) in solution. The intensity of the scattering also provides information on the arrangement of polymer segments.
	Small angle neutron scattering (SANS)	Provides access to the radius of gyration, but may also disclose more accurate information than SAXS. The location of the ending groups has also been determined by SANS experiments conducted with PAMAM dendrimers and PPI dendrimers.
	Laser light scattering (LLS)	It determines the hydrodynamic radius of dendrimers. Dynamic LLS is mostly used for the detection of aggregates.
C	**Microscopy methods**	Microscopy methods for characterization of dendritic polymer are [35, 36]
	Transmission microscopy	Electron or light produce images that intensify the original, with a resolution eventually limited by the wavelength of the source.
	Scanning microscopy	It produces an image by touch contact Q at a few angstroms of a sensitive canilever arm with sample. Ex. Atomic force microscopy.
D	**Size exclusive chromatography**	It allows the partition of molecules according to size.[37]
E	**Electrical techniques**	Electrical techniques for characterization of dendritic polymer are as follows [38-40]
	Electron paramagnetic resonance (EPR)	Quantitative determination of the substitution effectiveness on the surface of PANAM dendrimers.
	Electrochemistry	It provides information about the possibility of interaction of electroactive end groups.
	Electrophoresis	It provides the information about the assessment of purity and homogeneity of several types of water soluble dendrimers.
F	**Rheology and Physical properties**	Rheology and physical properties used for characterization of dendritic polymer are as follows [41-44]
	Intrinsic viscosity	It is as analytical probe of the morphological structure of dendrimers.
	Differential scanning calorimetry (DSC)	It used to detect the glass transition temperature depends on thy moleculer weight, entangment and chain composition of polymers.
	Dielectric spectroscopy (DS)	Gives complete information about molecular dynamic processes (α-, β)
G	**Miscellaneous**	Other methods used of characterization of dendritic polymer are as follows [45-47].
	X-ray Photoelectron Spectroscopy (XPS)	It provides detailed information about chemical composition of dendrimers such as poly (aryl ether) dendrons or PAMAM dendrimers which was obtained using XPS. This technique is most generally used for the characterization of layers.
	Sedimentation	Technique used for lactosylated PAMAM dendrimers, measurements of dipole moments for PMMH dendrimer.
	Titrimetry	It is used for determining number of NH2 end groups of PAMAM dendrimers.

Table 5
Major Technologically Important Factors

S.No.	Drug	Therapeutic activity	Solubility of Drug	Inference
1.	Artemether	treat multi-drug resistant strains of malaria	Poor solubility	Solubility improvement between factors 3-fold to 15-fold has been observed, depending on concentration and size of the dendritic micelles [91].
2.	Camptothecin	anticancer drug to facilitate damages DNA, and lead to cell destruction	very low water solubility and adverse side effects	A newly developed dendrimer platform, (PEHAM) poly (etherhydroxylamine) dendrimers, employed to enhance the water solubility of camptothecin [91].
3.	Ketoprofen	It belong to the propionic acid class of NSAIDs	Poor solubility and bioavailability	The occurrence of PAMAM dendrimers enhanced the transdermal delivery of ketoprofen [92].
4.	Methotrexate	An antimetabolite and antifolate drug used for treatment of many cancers, acts by inhibiting the metabolism of folic acid.	High dose of MTX used in Chemotherapy that can cause toxic effects to the rapidly dividing cells of bone marrow and Gastrointestinal mucosa.	Methotrexate has been encapsulated into generations 3 and 4 PAMAM dendrimers, to modify bioavailability and toxicity [91].
5.	Naproxen	used to reduce the severe pain, fever, Inflammation and stiffness.	Low soluble	The solubility of naproxen was considerably enhanced by the association with PAMAM dendrimers [91].
6.	Paclitaxel	anticancer drug	poor water soluble	PTX encapsulation into polyglycerol dendrimers resulted in improved water Solubility compare to the pure drug [93].
7.	Silver salts	antimicrobial activity	Low soluble	The encapsulation of silver salts within PAMAM Dendrimers showed conjugates exhibit slow silver release rates and antimicrobial activity against different Gram positive bacteria [94].

Dendrimers for additives, printing inks and paints:

Dendrimers can be used in toners material with additives, which required less material than their liquid counterparts. Xerox Corp. Patented a dry toner compound dendrimers as charge increasing species in the form of preservative [75]. Using preservative in printing inks, dendritic polymers certify to uniform linkage of ink to polar and non-polar foils. Use of Dendrimer additives in the composition of the innovation is efficient for varying the surface characterization of thermo plastic resin after moulding. One of example for this is polycarbonates, which are extensively used as an engineering thermoplastic for providing an exclusive grouping of toughness, rigidity, high softening temperature and processibility**.**

Dendrimers in light harvesting material:

An important research has been of great attention for designing molecules with controlled movement of charges. Most of the literature account shows direction towards energy funnelling from the chromospheres in the periphery to other chromospheres at the core [75]. A study on π-conjugated dendrimers family based on truxene and thienylethynylene were manufactured.

Dendrimers as Catalyst:

Dendritic polymers have been used in large amount as catalyst. There are two most important reasons for the benefit of using dendritic polymers. One of the reasons is opportunity of creating a large dendrimer with many active sites. These types of catalyst are an in-between heterogeneous and homogeneous catalyst which can be removed easily by filtration [76]. The second important reason is that, there is option of encapsulating a single catalytic site whose performance can be improved by dendritic superstructure [77]. Cooper and co-workers [78] synthesize fluorinated dendrimers which are soluble in supercritical CO2 that can be used to extract powerfully hydrophilic compounds from water into liquid CO2.

Dendrimers as Bio-mimics:

Dendrimers having their well distinct macromolecular dimensions and compartmentalized structure are ideal mimic for an extensive variety of bio-molecules. Dendrimers have capability to rendering the multivalent surface for improved binding of bio-molecules. Also, dendrimers have capability to generate a micro environment inside the dendrimer, which provides artificial catalytic sites or cavities possessing different properties for building of enzyme mimics. They are flexible and have cavities to accommodate solvent to act as host compounds for guest material. By using dendrimers more favourable merits compared to naturally happening proteins can be identified. More compactly packed structure compared to the natural proteins, for example certain peptide based dendrimer show an important increased resistance in the direction of proteases [79]. (According to Diederich et al) Dendritic porphyrin-metal complexes consist of elastic dendritic poly (ether amide) units [80]. Study of first and second generations of this dendrimer exposed that the decrease potential is moved towards positive values, than adequate shielding is obtained.

Dendrimers as a separating agent:

A study of diversity of compounds manufactured to determine suitability for attractive boron rejected by reverse osmosis and nanofilteration membrane to divide born from sea water has been developed. For separation, compound has amphiphile chemical structure and develops micelle in aqueous solution. As a new molecule dendrimers with a high density of functional moiety, are allow to form micelle structure which can be easily detached and improved by ultra filtration membrane. These micelles offer high functional density at the surface of the particle, high surface area and ease of partition for separation and regeneration of the compound. Polyamidoamine (PAMAM) dendrimers are used as chelating agents for the elimination of certain metal ions from waste water and from contaminated soil [81]. Other customized chelating PAMAM and poly (propyleneimine) dendrimer are also reported to be good ligands for a variety of hard metal cations [82] or can be describe as nanosponges for the elimination of Polycyclic aromatic hydrocarbons [66] and other particles [83].

Dendrimers as an Optical Sensing:

The necessity for improving sensor proceeding is always approaching towards explores new materials. Subsequent the birth of dendrimers, the opportunity was recognized by means of improving optical sensor technology. More important aspects are their two most important structural properties i.e. 3D structure and numerous terminal functional groups. Introduction to dendrimers is provided with the focus on PAMAM dendrimers and optical sensors. Current trends have been analyzed in those PAMAM dendrimer-based optical sensors used for pH, cations, and other analyte detection [84].

Dendrimers for siRNA Delivery:

The sighting of the “starburst polymer”, afterward renamed as dendrimer, this course group of polymers has gained significant consideration for various biomedical applications, mostly to the sole characteristics of this macromolecule, counting its monodispersity, uniformity, and the incidence of numerous functionalizable fatal groups. In current years, dendrimers have been deliberate broadly for their probable application as carriers for nucleic acid therapeutics, which exploit the cationic charge of the dendrimers for efficient dendrimer-nucleic acid concentration. siRNA is considering a promising, versatile tool amongst various RNAi-based therapeutics, which can efficiently regulate gene appearance if deliver effectively inside the cells [85].

Advantages of Dendrimers:

1. Dendrimers reveal a structural homogeny and monodispersity:

Dendrimers have concerned much interest because of their attractive structure and distinct properties [86]. Dendrimers are globular, size monodisperse, macromolecules in which all bonds appear radially from a middle focal point or core with a expected branching pattern and with repeated units that each contribute a branch point.

2. For enhanced targeting efficiency due to the presence of functional groups on the dendrimer: [87]

Earlier research shows that water-soluble synthetic polymers conjugate with antibodies or their fragments offer a potential targetable drug carrier system facilitates exact delivery of anti-cancer drugs to model tumours or tumour cells immunize into mice. A condition for the biological activity of the conjugate is addition of the drug to the polymer carrier via biodegradable spacer enable drug release at its target.

3. Surface alteration may authorize dendrimer mimicking biological exo- receptors, substrates, inhibitors or cofactors:

The comparison of dendrimers structure with 1gM antibodies (pentamers radially distributed) advise that they may be used to function as antibodies e.g. activation of macrophages, recognition, and high

attraction to antigen. Dendrimers have the aptitude to deliver drug within the cell or they may recover intracellular trafficking polymers which are connection when the drug is released. Dendrimers has constrained toxicity and immunogenicity but superior biodegradability [88]. They have better colloidal, biological and shelf-stability. They may be basically anticancer agents in nature due to interferon tumour necrosis factor inducing properties of acrylates, Baker and his colleagues use poly (amidoamine) dendrimers to transport anticancer drugs [89].

Targeted CT imaging of human hepatocellular carcinoma by applying low-generation dendrimer-entrapped gold nanoparticles adapted by means of lactobionic acid:

Improvement of cost-effective nanoscale contrast agents for targeted tumor CT imaging still remains a great challenge. The fusion of dendrimer-entrapped AuNPs (Au DENPs) with generation 2 (G2) poly (amidoamine) dendrimers pre-modified with fluorescein isothiocyanate by means of thiourea linkage and lactobionic acid (LA) through polyethylene glycol (PEG) spacer as template. The Au DENPs were characterize by using different techniques and were use as a nanoprobe for embattled CT imaging of hepatocellular carcinoma (HCC). The LA-modified Au DENPs with imply Au core size of 1.8 nm are water-dispersible, have colloidal stablility under different temperature (4-50 oC) and pH (5-8) environment, and also have cytocompatible in the deliberate concentration range. The developed LA-Au DENPs are capable for using as a nanoprobe for targeted CT imaging of HepG2 cells in vitro and the xenografted tumor model in vivo. With the confirmed organ compatibility, the developed LA-Au DENPs with low-generation dendrimers as templates might hold huge pledge to be used as a highly competent and money-spinning nanoprobe for targeted CT imaging of HCC [90].

Future prediction that Identifies and quantifies current and future promotion opportunities for nano-enabled drug delivery: [13]

It examines the business prediction for new delivery materials and methods, tools, and end-user applications being enabled by developments in nanotechnology such as:

- **identifies key issues in the commercialization process:**

This includes information on the general business climate for start-ups and big pharma, fundraising strategies and caveats, how companies were determining the intellectual property landscape, potential litigation issues, and possible exit scenarios for investors in related companies.

- **defines current and future applications for nanotechnology in drug delivery:**

It is widely apparent that nanotechnology will have a deep effect on the pharmaceutical industry. The report aims to highlight the chief nano-enabled drug delivery technology that are commercially available or under development.

- **analyzes the efforts of companies in nano-enabled drug delivery:**

Greatly difficulties in commercializing new technologies lie in execution. The report comments on various collaborations, planned alliances and/or partnerships with pharmaceutical companies, academic research institutions and biotechnology companies. Such partnerships are essential for the success of nano-enabled drug delivery companies.

- **appraise support mechanisms for nanotechnology in pharmaceutical environment:**

There are numerous sources of assets available for R&D counting traditional and corporate venture capital, debt financing, sponsored research and non-recurring engineering resources, federal & state grants etc. The statement addresses some of the regulatory issues and funding policies that are disturbing the growth of nanotechnology and nano-enabled drug delivery on a worldwide scale.

Forecasts the market for new technologies broken down by drug delivery type and technology stand:

Area enclosed which includes encapsulation technologies, implantable delivery methods, imaging agents and micro needles. Technologies include dendrimer, nanotubes and fullerenes, nanoparticles, quantum dots and magnetic/electrical targeting methods.

ENCAPSULATION OF DRUGS INTO DENDRIMERS: One of the important approaches to control the rate of drug release from the inclusion complexes is to encapsulate them into an envelope to slow release of drug to the target. Dendrimer used to encapsulate the targeted drug to increase the stability, modifies bioavailability, enhanced the delivery of drug, improve solubility and show conjugation with other drugs. Some drugs which have been encapsulated by dendrimer are listed in the table 5.

Dendritic consequence illustrated with phosphorus dendrimer:

The dendrimer outcome is pragmatic when functional groups behave in a different way, when it is unaided or connected to a dendrimer; its properties can even differ depending on the generation of the dendrimers. The dendritic effect can be pragmatic with every type of dendrimer, and for any type of property, yet if it has been usually tracked in catalysis and biology, and to a smaller amount in the field of materials. This type of work is mostly slanting towards the various types of dendritic possessions observed with polyphosphorhydrazone dendrimers [95].

CONCLUSION

Due to their exclusive manner dendrimers have improved physical and chemical properties. The elevated stage of control over the structural design of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds an ultimate carrier in biomedical application such as drug delivery, gene transfection and imaging. These properties construct the dendrimers a smart choice for drug delivery application and improve the solubility of poorly soluble drug. This review of dendrimer provides complete information about drug carrier, clearly identifies the prospective of this novel ―fourth building class of polymers‖ and confirms the high buoyancy for the future of dendrimers in pharmaceutical field. These inimitable physical and chemical properties of dendrimer have demonstrated immense versatilities in variety of applications. Also further studies are needed to recognize their absorption, uptake mechanisms by biological membranes and in-vivo stability. Dendrimers have successfully used in medicinal applications such as diagnostic tools and ultimately in drug delivery.

Acknowledgement: The authors wish to thank Dr. Pushpendra K. Tripathi (Director), Department of Pharmacy, Rameshwaram Institute of Technology & Management, Lucknow, for their kind support and encouragement to carry out this work.

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