A review on dendrimers: a new class of nanoscale polymers

Abstract:

Dendrimers are hyper-branched macromoleculeshaving tree like structure, consisting of a core molecule and alternating layers of monomers. Due to their unique architecture these have improved physical and chemical properties like high solubility, miscibility and reactivity. Dendrimers consist of well defined size, shape, molecular weight and monodispersity. These properties formulate the dendrimers a suitable carrier in drug delivery application. These are built from number of molecular entities of colloidal paticles that exists in equilibrium with the molecules or ions in nature and due to these increases the solubility of poorly soluble drugs.

This review gives concise information about the dendrimers, its synthesis, characterization and application in drug delivery.

This review provides information about the dendrimers, their synthesis, characterization and their potential use in a range of areas of research,technology and treatment.

Key words: Dendrimers, monomers, solubility enhancement, drug delivery.

Introduction

At present scenario many researchers are working todeliver the drug with improved bioavailability, enhancement in solubility, to hit the target site to produce therapeutic effects, and to avoid the toxic effects[1]. Dendrimers is one out of many approaches which focuses on the above criteria. These are hyper-branched, globular, monodisperse, three dimensional nanoscale synthetic polymers, having very well defined size, shape and definite molecular weight having high degree of surface functionality and versatility[2].

The term “Dendrimer” derived from two Greek words “Dendron” meaning tree “Meros” meaning part. The chemistry of dendrimers was introduced in 1978 by Fritz Vogtle and co-workers. Dendrimers used as a polymeric material. Dendrimers differs from traditional polymers in that they have a multi-branched, three dimensionalarchitecture with very low polydispersity and high functionality[3].

In dendritic structures number of terminal group increases exponentially with a linear increase in the generation of dendrimer. This relationship limitsthe ultimate size of the dendrimer due to steric crowding of the terminal groups.

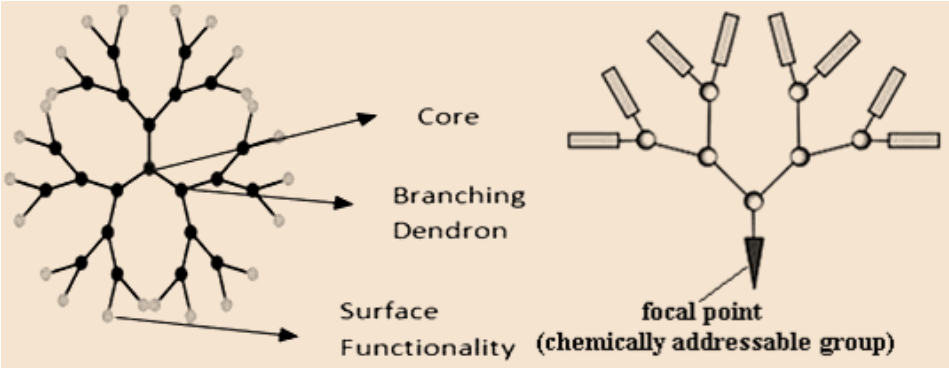


Fig.1: (a) Dendrimers (b). Dendron

Dendrons is the term used about a dendritic wedge without a core, the Dendrimer can be prepared from assembling two or more dendrons. As we shall see later, dendrons are very useful tools in the synthesis of dendrimers by the segment couplingstrategy. These dendrons have been used in the creation of numerous of dendrimers having different structures and functions. The

dendrimer shell is the homo-structural spatial segment between the focal points, the "generation space". The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred to as the dendrimer interior[4].

In dendrimers, the outer shell consists of a varying number ofpincers created by the last focal point before reaching the dendrimer surface.

Advantages

1. Low polydispersity index:

Due to stringent control during synthesis, they have lower polydispersity index. As the density of branches increases the outer most branches arrange themselves surrounding a lower density core in the form of spheres and outer surface density is more and mostof the space remains hollow towards core. This region is utilized for drug entrapment[5].

2. Improved permeability

Dendrimers can cross bio barriers like blood brain barrier, cell membrane. Dendrimers might show an enhanced permeability and retention effect whichallows them to target tumour cells more effectively than small molecules[6].

3. Improved loading capacity

Drug can get entrapped inside the internal cavities as well as electro statically in the surface of dendrimers. Dendrimers structures canbe used to load and store a wide range of organic or inorganic molecules by encapsulation and absorption on surface[7].

4. Higher Solublization Potential

Dendrimers improves the solubility, biodistribution, and efficacy of a number of therapeutics as well as being used as imaging and diagnostic molecules in animal models bearing brain tumors. Probable mechanism includes ionic interaction, hydrogenbonding and hydrophobic interactions[8].

***5.* Increased permeability and retention effect**

Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectivelythan small molecules[9].

6. High stability

Dendrimers have nanoscopic particle size range from 1 - 100 nm, which makes them less susceptible for reticulum endothelium uptake. Dendrimers drug complex or conjugate shows better colloidal, biological and shelf-stability[10].

7. High uniformity and purity

Dendrimers have uniform sizes range, well defined surfacefunctionality, and negligible impurity.

8. Low immunogenicity

Dendrimers shows low or negligible immunogenic response when injected or used topically. The problems as found in vesicular system like chemical instability, drug leakage, aggregation and fusion during storage, solubility in physiological environment, lysis ofphospholipids, purity of natural phospholipids are not present in dendritic system

9. Sustained/ extended effect

Dendrimers releases drug in a sustained manner.

10. Multifunctional platform

Multiple functional groups are present on outer surface of dendrimers, which can be used to attach vector devices for targeting to particular site in the body.

Terminal groups may also be modified to reorganize specific receptors. Thesurface modification may allow designing dendrimers mimicking biological exo-receptors, substrates, inhibitors or cofactors[11].

11. Low toxicity

Most dendrimers systems display very low cytotoxicity levels but have good biodegradability.

Types of Dendrimers:

1. Poly amidoamine dendrimers (PAMAM)

Dendrimers: PAMAM dendrimers represent an exciting newclass of macromolecular architecture called "dense star" polymers. They have two-dimensions, star like pattern. These are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. These dendrimers are commercially available, usually asmethanol solutions[12].

2. Hybrid dendrimers

Hybrid dendrimers are hybrids of dendritic and linear polymers. These are obtained by complete mono functionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic self organized lattices that are less readily available from other modified dendritic structures[13].

3. Fréchet-Type Dendrimers:

It is a more recent type of dendrimer based on poly-benzyl etherhyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalization, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media[14].

4. Tecto Dendrimers:

These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition,diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy[15].

5. Chiral Dendrimers:

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Their potential use includes as chiral hosts for enantiomeric resolutions and as chiral catalysts for asymmetricsynthesis[16].

6. Multiple Antigen Peptide Dendrimers:

It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer used in biological applications, *e.g.* vaccine and diagnostic research[17].

7. Micellar Dendrimers:

Micellar dendrimers are unimolecular water soluble hyper branchedpolyphenylenes micelles.

8. Amphiphilic Dendrimers:

They are built with two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing[18].

9. Propylene Imine (PPI) Dendrimers:

These dendrimers are generally poly-alkyl amines havingpoly-alkyl amines as end groups, and numerous tertiary trispropylene amines present in interior portion. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology[19].

10. Poly amidoamineorganosilicon (PAMAMOS) dendrimers

These are radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) having inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These are excellent in networks regularity and have ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, lectronics,

photonics, chemical catalysis etc. Thesedendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains[20].

Properties of dendrimers

1. Size and shape

Dendrimers shows improved physical and chemical properties due to their molecular architecture. The dendrimers shape depend on the generation i.e. lower generation shows open planar elliptical shape while highergeneration shows compact-spherical shape. Inherent structural defects exists when synthesizing high-generation dendrimers. The reasons include incomplete reactions and steric resistance, which cause the missing of repeating units, intramolecular cyclization, dimmer formation and retro- Michael reaction in dendrimers. Due to their nanometric scales and other properties that are similar to proteins, dendrimers are also known as artificial proteins. The dendrimer can be controlled by molecular engineering so that its size resembling to antibodies, enzymes and globular proteins[21].

2. Monodispersivity,

The monodispersion means that the dendrimers has a well defined molecular structure and without large individual variations, inother words, they are homogeneous unlike other polymers due to their controlled synthesis and purification processes. Dendrimers are monodisperse in nature i.e. they have isomolecular species, whose molecular size, shape and disposition of organic moieties are adjusted and controlled. Monodisperse property of dendrimers has already been extensively characterized by high performance liquid chromatography, size exclusion chromatography, mass spectrometry, gel electrophoresis,and transmission electron microscopy[22].

2. Polyvalency

It shows the outer arrangement of reactive groups onthe exterior of dendrimer nanostructure. Polyvalency it provides for versatile functionalization; it produce multiple interactions with biological receptor sites, for example, in the design of antiviral therapeutic agents.

The polivalency is related to the quantity of reactive sites on outside of the dendrimer potential to form connections with various materials of interest. The multivalencyallows better interaction with biological targets since most of the molecularinteractions occur through biological multivalent bonds[23].

3. Solubility and biocompability

The solubility of dendrimers is determinedby the surface functional groups, dendrimer generation, repeated units, and even the core. Generally dendrimers have greater solubility in common solvents as compared to linear polymers. If the surface end groups are hydrophobic in nature, then dendrimers are soluble in nonpolar solvent. Ifthe surface end groups are hydrophilic in nature and dendrimers are soluble in polar solvent[24].

4. Toxicity

Some dendrimer systems display very low toxicity levels – with dendrimers carrying anionic groups being less toxic than those carrying cationic groups. Dendrimers may cause toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytictoxicity and cytotoxicity. Therefore, PAMAM dendrimers are more cationic than anionic cytotoxic. Many toxic effects of dendrimers are attenuated at their surfaces with hydrophilic molecules and poly (ethylene glycol) (PEG) which masks the surface charge cationic dendrimers improving biocompatibility and increasing the solubility of the polymers[25].

5. Drug and dendrimers interactions

Dendrimers interact with drug molecules physically byabsorption on surface by electrostatic interactions or by conjugation with the surface groups for covalent bonding or by encapsulation of the drug into the cavities of the dendrimers. In most cases, however, the conjugated dendritic assembly functions as pro-drug ‘where, upon internalization into the target cell, the conjugate must be liberated to activate the drug.

6. Viscosity

In solution dendrimers form a tightly packed ball, that influences its rheologicalproperties. The intrinsic viscosity dendrimers solution does not exhibit linear relationship with mass[26].

7. Immunogenicity:

It is one of the crucial biological properties of the dendrimers. As per research, unmodified amino terminated PAMAM dendrimers are presenting no or only weak immunogenicity of the G3–G7. PAMAM dendrimers with polyethylene glycol chains decreaseimmunogenicity and offers longer lifetime in the blood stream in comparison to un-modified dendrimers.

8. Loading capacity (molecular container property)

This property makes dendrimers very suitable as drug delivery vehicles and also appropriate for obtaining electro-optic or magnetic devices. In addition to carrying materials on their surface, the internal cavities of dendritic structures can be used to carry and/ orstore a wide range of metals, organic, or inorganic molecules by encapsulation and absorption. The appropriate type (and degree) of functionalisation will results in the desired loading capacity[27].

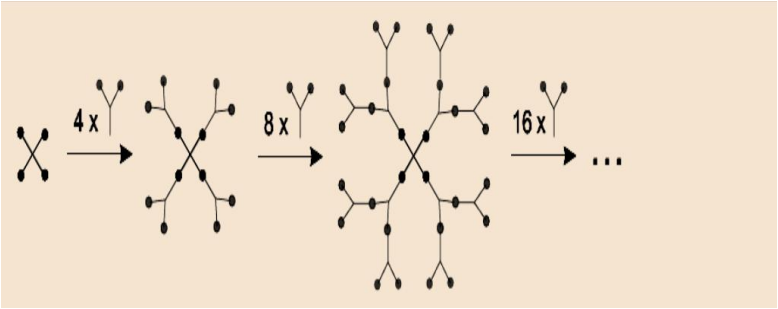
Methods of dendrimer synthesis:

There are two different methods of dendrimer synthesis, divergent synthesis and convergent synthesis .

1. Divergent Method:

In this method, dendrimers grows outwards from the focal core, using a pair of basic operations that consist of coupling of building blocks, and de protection ormodification of end functionalities of the periphery to create new reactive surface functionalities; this pair of basic operations is often referred to as the growth of a generation. 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). This process is repeated until the desired number of generations is obtained.

In this method very large dendrimers get prepared. Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To minimizethese side reactions and imperfections, it’s recommended to use a large excess of reagents[28].



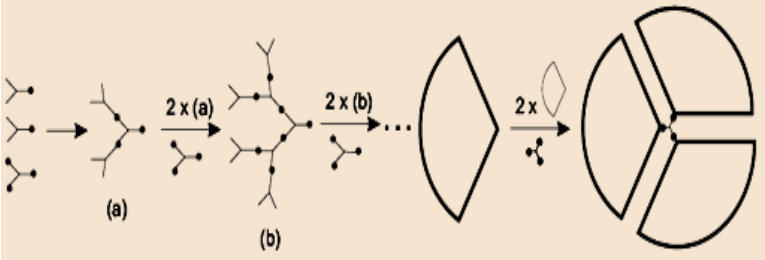
The divergent method

2. Convergent Method:

It is an alternative method to the divergent approach for producing precisely controlled dendritic architectures. The convergent approach overcomes some of theproblems associated with the divergent method. In the convergent approach, the dendrimer is constructed stepwise. Starting

from the end groups and progressing inwards. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule.

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. The convergent approach does not allow the formation of high generations because steric problems occur in the reactions of the dendrons and the core molecule. Reactions under a convergent approach need a relatively longer time compared to that of the divergent method[29].



The convergent method

Factors affecting dendrimers synthesis:

There are different factors which can affect dendrimer synthesis. Thenon-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.

Characterizations of dendrimers:

Techniques and methods for characterization of dendrimers

1. Spectroscopy techniques[30]	**a). NMR:** Used for analysis of size, morphology and dynamics of dendrimers for organic dendrimers such ad ppi, polyphenylester. **b). UV-Vis method:** Used to monitor synthesis of dendrimers. **c). Infra red spectroscopy:** For routine analysis of the chemical transformations occurring at the surface of dendrimers. d). **Fluorescence:** To quantify defects during the synthesis of dendrimers. **e). X-ray diffraction-** For determination of the chemical composition, structure, size and shape of dendrimers. **f). Raman spectroscopy** gave relevant information about the degree of cyclodehydrogenation of polyphenylene dendrimers, and the characterization of PPI and dendrimers. **g). Infra red spectroscopy (IR)-** for routine analysis of the chemical transformations occurring at the surface of dendrimers.
2) Microscopy[22]	Transmission microscopy and Scanning microscopy are mainly used for dendrimer analysis.
3)**Chromatography**[25]	Size exclusive or gel permeation chromatography allows the separation of molecules according to size.
4) **Electrical techniques**[31]	**a). Electron paramagnetic resonance (EPR)** Quantitative determination of the substitution efficiency on the surface of PANAM dendrimers. **b). Electrochemistry** gives information about theMpossibility of interaction of electroactive end groups.

	c). Electrophoresis used for the assessment ofpurify and homogeneity of several type of water soluble dendrimers.
5) **Rheology, Physical properties**[28]	**a). Intrinsic viscosity-** used as analytical probe of the morphological structure of dendrimers. **b). Differential scanning calorimetry (DSC)-** used to detect the glass transition temperature which depends on the moleculer weight, entangment and chain composition of polymers. **c). Dielectric spectroscopy (DS)-** gives information about molecular dynamic processes (α-, β)

Appliapplications of dendrimers

Specific properties such as unparalled molecular uniformity, multifunctional surface and presence of internal cavities makes dendrimers suitable fora variety of high technology uses and are as follows:

(A) Pharmaceutical applications

1. Dendrimers in ocular drug delivery

The nanosize, ease of preparation, functionalization, and possibility to attach multiple surface groups renders dendrimers as suitable alternative vehicle ofophthalmic drug delivery.

PAMAM dendrimers with carboxylic or hydroxyl surface groups, improves residence time and enhance bioavailability of pilocarpine in the eye. Also some of the phosphorus containing dendrimerswith quaternary ammonium core and terminal carboxylic groups has successfully reported for ocular drug delivery of carteolol[32].

2. Dendrimers in pulmonary drug delivery

Dendrimers have also been reported for pulmonary drug delivery as well. A previous study was performed, by measuring plasma anti-factor Xa activity using PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin, and by observing prevention efficacy of deep vein thrombosis in a rodent model. it was observed that G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability ofEnoxaparin by 40% while G2.5 PAMAM half generation dendrimers containing negatively charged carboxylic groups had no effect[33].

3. Dendrimers in transdermal drug delivery

Dendrimers may improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently due to it's highly water soluble and biocompatible nature. The viscosity imparting property of a dendrimer solution allows for ease of handling of highly concentrated dendrimer formulations forthese applications. Drug permeation can be improved through the skin when PAMAM dendrimer complex with NSAIDs like ketoprofen, diflunisal and enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application[29].

4. Dendrimers as Nano-Drugs

Dendrimers as nano-Drugs, useful as antiviral drugs against the herpes simplex virus can potentially prevent/reduce transmission of HIV and other sexually transmitteddiseases (STDs) when poly (lysine) dendrimers modified with sulfonated naphthyl groups.

5. Dendrimers for controlled release drug delivery

Encapsulation of 5-fluorouracil into PAMAM dendrimers(G=4) modified with carboxy methyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity. Controlled release of the Flurbiprofen achieved by formation of complex with amine terminated generation 4 (G4) PAMAM dendrimers[26].

6. Dendrimers in oral drug delivery

Oral drug delivery studies using the human colon adenocarcinoma cell line, which have indicated that low generation PAMAM dendrimers cross cell membrane through acombination of two processes, i.e. paracellular transport and adsorptive endocytosis. Increase in the cytotoxicity and permeation of dendrimers when increase in the concentration and generation[28].

7. Dendrimers as bio mimetic artificial proteins

Dendrimers are often referred to as "artificial proteins" due to their dimensional length scaling, narrow size distribution, and other bio mimetic properties. For examples PAMAM family, they closely match the sizes and contours of many important proteins and bioassemblies like insulin (3 nm), cytochrome C (4 nm), and haemoglobin (5.5 nm) are approximately the same size and shape as ammonia-core PAMAM dendrimers generations 3, 4 and 5, respectively.

8. Dendrimers as solubility enhancer

Dendrimers are unimolecular micellar nature, due to have hydrophilic exteriors and hydrophilic interiors and form covalent as well as non-covalent complexes with drug molecules and hydrophobes, and enhance its solubilisation behaviour. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial propertiesThese characteristic offers the opportunity to solublepoorly soluble drugs by encapsulating them within the dendritic structure not have a critical micelle concentration[29].

9. Dendrimers in targeted drug delivery

Dendrimers have attracted the most attention as potential drug delivery scaffolds due to their unique characteristics. Dendrimers can be used to deliver drugs either by encapsulating the drug in the dendrimer interior void spaces or by conjugation to surface functionalities. Dendrimers have ideal properties which are useful in targeted drug-delivery system.For example PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively[30].

10. Dendrimers in targeted gene delivery

Dendrimers are extensively used as non-viral vector for gene delivery. They can work as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier. PAMAM dendrimers have also been tested as genetic material carriers. Cationic dendrimers (Polypropylenimine (PPI) dendrimer) deliver genetic materials into cells by forming complexes with negatively charged genetic materials throughelectrostatic interaction. Furthermore, dendrimers are non-immunogenic and are thus uniquely suited as carrier structures for drugs or bioactive molecules without degradation in immune system[31].

(B) Therapeutic application

1. Dendrimers in anticancer drug delivery

One of the major applications of dendrimers is as a delivery vehicle for various anticancer drugs. The structure and tunable surface functionality of dendrimers allows for the encapsulation/conjugation of multiple entities, either in the core oron the surface, rendering them ideal carriers for various anticancer drugs. This dendritic nano-formulation, which contains doxorubicin covalently bound through a hydrazone linkage to a high molecular weight three-arm polyethylene oxide; exhibits reduced cytotoxicity in-vitro. In an attempt to improve the efficacy of doxorubicin, Lai *et al* utilize photochemical internalization (PCI) technology for site-specific delivery of membrane impermeable macromolecules from endocytic vesicles into the cytosol. Many investigators have also explored the feasibility of cisplatin incorporation in dendrimers[32].

2. Dendrimers for boron neutron capture therapy

The radiation energy generated from the capture reaction of low-energy thermal neutrons by 10B atoms has been used successfully for the selective destruction of tissue.

This radiation energy has been used successfully for the selectivedestruction of tissue. Dendrimers are a very fascinating compound for use as boron carriers due to their well defined structure and multivalency[33].

(C) Diagnostic applications

1. Dendrimers as molecular probes

Dendrimers are fascinating molecules to use as molecular probes because of their distinct morphology and unique characteristics. For Example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integratedmolecular probe, because of their large surface area and high density of surface functionalities[34].

2. Dendrimers as X-ray contrast agents

Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin are used to obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary etc. In a study Krause and co-workers synthesized a number of potential dendritic X-ray contrastagents using various organo metallic complexes such as bismuth and tin[35].

3. Dendrimers as MRI contrast agents

A number of research groups have explored the use of dendrimers as a new class of high molecular weight MRI contrast agents. Introduction of target specific moieties to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer contrast agents, for example folate conjugated Gd (III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor. In a study Wiener *et al* synthesized a folate conjugated Gd(III)–DTPA PAMAM dendrimers, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor[36].

Conclusion:

Present review discussed very elobarately about characterization techniques and applications of dendrimers. The dendrimers have a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possessunique properties, such as high degree of branching, multi valency, globular architecture and well defined molecular weight, there by offering new scaffolds for drug delivery. They provide platforms for drug attachment and have the ability to encapsulate or bind drugs via several mechanisms. At present many drugs are facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs.

Review concludes that there is need of some more research on effects of dendrimers to remove the ambiguity about the safety of dendrimers and to make them an excellent substitute for polymers in the future as it is one of the youngest and excitingfields of polymers researches, where all branches of science can take part and hence, deserves more intensive attention.

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