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Dendrimers as a Potential Drug Delivery System: A Comprehensive Review

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ABSTRACT

Dendrimers are synthetic, highly branched, monodisperse macromolecules of nanometer dimensions with exact and large number of functional groups, distributed with unprecedented control, makes them a promising scaffolds, for drug delivery. Dendrimers serves as an ideal vehicle for cancer therapy, immunology, vaccines, antivirals, biosensors for diagnostics, neuron capture therapy, photodynamic therapy and photo thermal therapy. Dendrimers chemistry is one of the most fascinating and rapidly expanding areas in the field of chemistry. Prior to the dendrimer technology, nanoparticle drug delivery systems were one of the choicest systems owing to their selectivity and stability of therapeutic agents incorporated into the system. However, few drawbacks such as reticuloendothelial system (RES) uptake, drug leakage, immunogenicity, hemolytic toxicity, cytotoxicity, hydrophobicity etc., impede the usage of these nanostructures. Further, these shortcomings shall be circumvented by modifying the surface engineering, such as poly ester dendrimer, arginine dendrimer, glycol dendrimer, PEGylated dendrimers etc., Unique properties of uniform size, water solubility, modifiable surface functionality and availability of internal cavities makes them intriguing carrier for biological and drug delivery system. In the present review, we focused on the bioactive agents that can be easily encapsulated into the interior cavity (or) chemical attachment, conjugation (or) physically adsorbed on to the dendrimer surface to serve the desired properties of the carrier to cater specific needs of the active components, its characterization and application.

Keywords: Dendrimers, nanostructures, permeability, monomer, oligonucleotides.

INTRODUCTION

In these formative years of nanosciences, one of the most frequently attracted names in the scientific literature is a class of polymeric macromolecules, provides greater potential to provide tailored form with the realistic functions ever realized with regards to pharmacokinetics and targeted delivery. A macromolecular drug delivery system refers as a complex material within which the drug is attached to a carrier molecule, such as polymer, antibody and hormone. By modifying certain properties of the carrier the adsorption and distribution of the drug, protection from degradation and minimization of the side effects can be achieved. These polymerized macromolecules are named as 'dendrimers' and envisaged as the polymers of molecules, each of which generates a new chains, all of which converge to a single focal point or core. [1-4] In 1978, dendrimer chemistry was introduced. Dendrimers are repeatedly branched, globular

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macromolecules with many arms emanating from a central core [5-6], to which carbon and other elements are attached by repeating series of chemical reaction that leads to the constitution of spherical branding structures [Figure 1]. Many disadvantages such as poor solubility, bioavailability, permeability, biocompatibility and toxicity of a drug shall conveniently be circumvented using dendrimers. [7-9] Dendritic polymers provide a route to create very well defined nanostructures which are very much suitable for enhancing solubility of poorly soluble drug, delivering of oligonucleotide, targeting of drug to specific site and ability to act as a carrier for development of drug delivery system. [10-13] Dendrimers are synthetic, highly branched, spherical, mono-disperse macromolecules of nanometer dimensions developed by the iterative synthetic methodology. They possess an initiator core, interior layers composed of repeating units radially attached to the interior core, terminal core attached to the outer most interior generations. [14-19] Research has been continuing to improve the efficacy and lessen the cost in synthesizing these macromolecules. Dendrimers exhibit modifiable surface characters and internal cavities. These characters account for dendrimers to make fascinating for biological and drug delivery applications. [20-21]

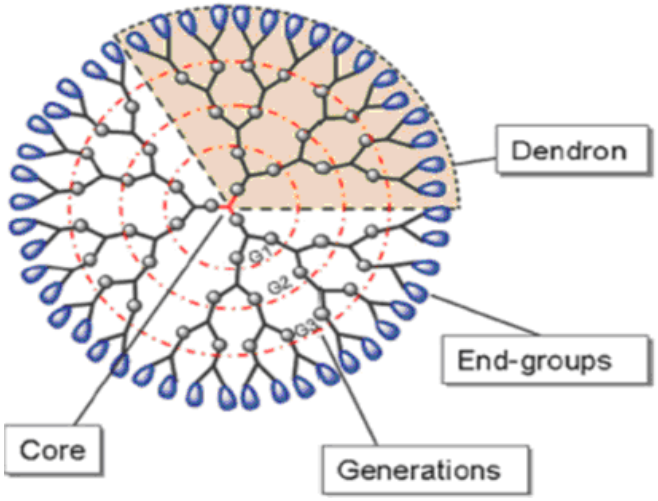


Fig. 1: Structure of Dendrimer

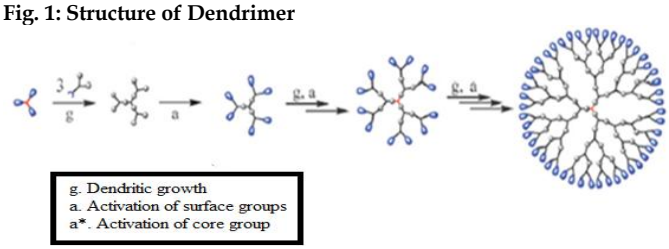


Fig. 2: Divergent dendrimer growth

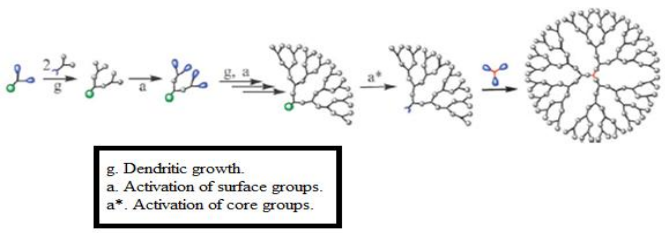
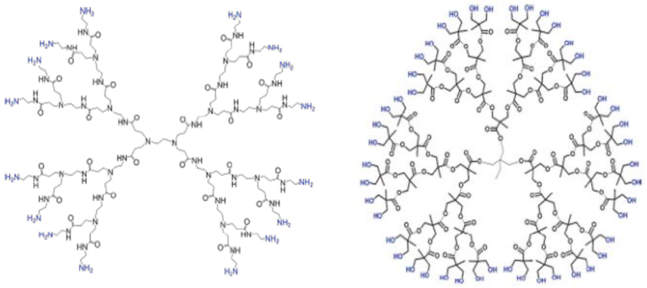
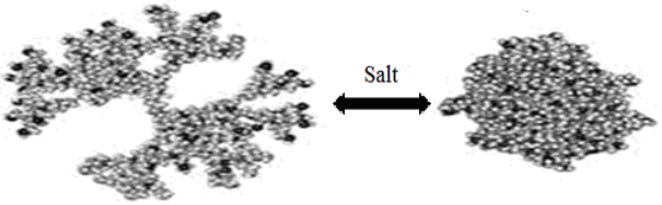


Fig. 3: Convergent dendrimer growth



(a) **(b)**

Fig. 4: (a) Second generation PAMAM dendrimer (b) Fourth generation PAMAM dendrimer



Low salt **High salt**

Fig. 5: Effect of salt concentration on the conformational change of PPI dendrimer

Synthesis of dendrimer

There are two defined methods, divergent and convergent synthesis involved for dendrimers. However, during the synthesis process, actual reaction consists of many steps needed to protect the active site. This warrants for the dendrimers cumbersome to make and expensive one.

Divergent method [22]

This process involves the growth of dendron (molecular tree) originates from a multifunctional core, which are extended outward by a series of reaction, most commonly Michael's reaction. This approach involves the assembling of monomeric modules in a branch-upon-branch design. This method is currently preferred for the commercial route for production [Figure 2].

Convergent method [23]

In this process, dendrimers are built from small molecules to form dendron molecular surface inward to a reactive focal point at the root. This leads to the formation of a single reactive dendron. Further, dendrimer structure was synthesized upon reaction of several dendrons with multifunctional group to attain a product. This method is convenient to remove impurities and shorter branches, so that the final dendrimers are monodisperse. Using these two techniques more than 100 different compositions of dextrins was synthesized [24-27] [Figure 3].

Components of dendrimers

Generation of dendrimer

It is a hyper branching, the centre of the dendrimer towards the periphery, results in homostructural layers between the focal points (branching points). The number of focal points on core towards the dendrimer surface is referred as the generation number. Starting with the central branched core molecule as generation 0 (G0) and increasing with each successive addition of branching points such as G1, G2 etc., dendrimers are

often characterized by their terminal generation, for eg G5, dendrimer refers to a polymer with four generation of branch points emanating from a central branched core with each successive generation, the number of end groups increases exponentially. Dendritic macromolecules tend to increase linearly in diameter to adopt a globular shape, with increase in dendrimer generation. Characterization of dendrimers was given in detail in Table 2.

Shell

It is the home-structural spatial segment between focal points and surface. The inner shells are referred as the dendrimer interior.

Pincer

In dendrimers, the outer shell consists of varying number of pincers formed by last focal point before reaching the dendrimer surface. Generally, the pincers represents half number of surface groups as the dendrimer chains divides into two chains in each focal point.

End group

It is also referred as the terminal or surface group of dendrimer. Dendrimers having the amine end groups are termed as amino-terminated dendrimers.

Types of dendrimers for drug delivery

PAMAM (polyamidoamine) dendrimers

They were first synthesized, characterized and commercialized for drug delivery [28] [Figure 4].

The majority of the studies one PAMAM dendrimers revealed that, PAMAM generations (G0-G10) displaying wide number of peripheral groups (4-4096), with different functional end groups such as amine, carboxylic, hydroxyl etc., with a different molecular weights (657-935000 g/mol). These dendrimers are biocompatible, non-immunogenic, water-soluble nature with terminally modifiable amino group that facilities linkage with host molecules. They possess distinct chemical structures and properties including hydrogen bonding, charge, toxicity etc., however, these properties shall be manipulated by increasing dendrimer generation or modifying surface groups. Recently, the research has been focused on the mechanistic and systematic area for better understanding or relationship between composition, architecture and properties of dendrimers towards the biocompatibility and pharmacokinetics such as biodistribution and excretion. Galdolinium, a contrast agent used in MRI, offers a greater contrast between normal and abnormal tissues in brain and body. Upon conjugation with folate-PAMAM dendrimer for targeting to tumour cells, increased the longitudinal relaxation rate of tumour cells expressing the hFR with specific targeting to ovarian tumour xenograft. Ester-terminated generation dendrimers of this category found to exhibit higher water soluble hydroxyl surface on reaction with tris. The study further revealed that the complexing these dendrimers with hydrophobic guest moiety, in turn becomes highly soluble at pH 7. But these complexes are found to be unstable at acidic conditions and leading to precipitation on exposure to pH 2, presumably due to the protonation of internal tertiary amines and causing the liberation of guest molecules. [29] Most of the research has been performed on modified poly amidoamine dendrimer generations of G0-G10 having 4-4096 functional groups such as hydroxyl, amine and carboxylic acid with a molecular weight ranging between 657-935000 g/mol. These dendrimers possess distinct chemical structures and properties of hydrogen bonding, charge, basicity etc.; however, these properties shall be altered by increasing the dendrimer generation or modifying the surface functional groups. Recently, research has been focused on the mechanistic approach for the better understanding the relationship between composition, architecture properties of dendrimers towards biocompatibility and pharmacokinetics including their biodistribution and excretion. [30] An increase of 33% gadolinium was observed per receptor from dendrimer complex as compared to gadolinium alone. Non-ionic folate conjugated PAMAM dendrimer labeled with fluorescein isothiocyanate for targeting to tumour cells expressing hFR (high affinity folate receptor). Methotrexate and taxol drug conjugates of these folate conjugated dendrimers investigated for their *in vivo* cytotoxicity and specificity of drug targeting. [31] On the other hand, another process of hFR targeting involves the surface modification on polyaryl ether dendrons and dendrimers. [32] In this method, folic acid is conjugated to surface hydrazides by active ester formation and EDC coupling strategy. An attempt has been made to improve the water solubility by attaching plly ethylene glycol (PEG) chain to free hydroxyl groups in the dendrons reduced the binding of folic acid with increased poly dispersity.

Tectodendrimer

They composed of a core, surrounded by group of dendrimers to perform a specific function such as smart therapeutic nanodevice.

Multilingual dendrimers

In these dendrimers, the surface contains multiple copies of a particular functional group.

Chiral dendrimers

The chirality in these dendrimers is based upon the construction of a constitutionally different but chemically similar branches attached to the chiral core.

Hybrid dendrimers linear polymers

These are hybrids either block or graft polymers of dendritic and linear polymers.

Amphiphilic dendrimers

They are built with two segregated sites of chain end, one half serves as an electron donating and the other half is electron withdrawing.

Micellar dendrimers: These are unimolecular micelles of water soluble hyper branched polyphenylenes.

Factors affecting the properties of dendrimers

Effect of pH

Amino-terminated PPI and PAMAM dendrimers have basic surface groups as well as a basic interior. For

these types of dendrimers with interiors containing tertiary amines, the low pH region generally leads to extended conformations due to electrostatic repulsion between the positively charged ammonium groups. Applying molecular dynamics to predict the structural behavior of PAMAM dendrimers as a function of pH show that the dendrimer has an extended conformation, based on a highly ordered structure at low pH (<4). [33] At this pH, the interior is getting increasingly 'hollow' as the generation number increases as a result of repulsion between the positively charged amines both at the dendrimer surface and the tertiary amines in the interior. At neutral pH, back-folding occurs which may be a result of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. At higher pH (>10), the dendrimer contract as the charge of the molecule becomes neutral, acquiring a more spherical (globular) structure, where the repulsive forces between the dendrimer arms and between the surface groups reaches a minimum. At this pH, the conformation has a higher degree of back-folding as a consequence of the weak 'inter-dendron' repulsive forces. [34]

Effect of solvent

The ability of the solvent to solvate the dendrimer structure is a very important parameter when investigating the conformational state of a dendrimer. Dendrimers of all generations generally experience a larger extent of back-folding with decreasing solvent quality, i.e. decreasing salvation. [35] However, being more flexible, the low generation dendrimers show the highest tendency towards back-folding as a result of poor solvation compared to the higher generation dendrimers. NMR studies performed on PPI dendrimers conclude that a non-polar solvent like benzene, poorly solvates the dendrons favoring intramolecular interactions between the dendrimer segments and back-folding. However, weakly acidic solvent like chloroform can act as a hydrogen donor for the interior amines in a basic dendrimer like PPI, leading to an extended conformation of the dendrimer because of extensive hydrogen bonding between the solvent and the dendrimer amines. Both experimental as well as theoretical studies on amino-terminated PPI and PAMAM dendrimers (polar dendrimers) show the tendency that nonpolar aprotic (poor) solvents induce higher molecular densities in the core region as a result of back-folding, whereas polar (good) solvents solvate the dendrimer arms and induce a higher molecular density on the dendrimer surface. Back-folding of the polar surface groups may expose the more hydrophobic dendrimer parts to the surroundings leading to a decreased surface polarity of the back-folded dendrimer.

Effect of salt

High ionic strength (high concentration of salts) has a strong effect on charged PPI dendrimers and favors a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor salvation. At low salt conditions, the repulsive force between the charged dendrimers segments results in an extended conformation in order to minimize charge repulsion in the structure [35-36] [Figure 4].

Effect of concentration

Dendrimers with flexible structures the conformation is not only affected by small molecules like solvents, salts or protons, but may also be sensitive to larger objects, such as other dendrimers or surfaces which can have a great effect on the molecular density and conformation of the dendrimer. Small angle X-ray scattering (SAXS) experiments performed on PPI dendrimers (G4, G5) in a polar solvent like methanol show that the molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted. This molecular contraction may minimize the repulsive forces between the dendrimer molecules and increase the ability of the dendrimers to exhibit a more tight intermolecular packing. [37]

Pharmaceutical applications of dendrimers [38-40]

Table 1: Various drugs incorporated into dendrimers and their routes of administration

S. No	Routes of Administration	Dendrimer	Drug
1.	IV	PEGylated PAMAM dendrimer Galactose-coated PPI dendrimer	5-Fluorouracil, Primaquine phosphate
2.	IM	Polyester dendrimer PEGylated peptidedendrimer	Doxorubicin, Artemether
3.	Transdermal	PAMAM dendrimers	Tamsulosin, Indomethacin
4.	Ophthalmic	PAMAM dendrimers	Tropicamide, Pilocarpine
5.	Oral	PAMAM dendrimers	5-Fluorouracil

Ocular drug delivery

Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability.

Pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery of enoxaparin. G_2 and G_3 generation positively charged PAMAM dendrimers increased the relative bioavailability of enoxaparin by 40%.

Transdermal drug delivery

Dendrimers designed to be highly water soluble and biocompatible materials that have been shown to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen and Diflunisal) improved drug permeation through the skin.

Table 2: Characterization of dendritic polymer

S. No.	Methods	Characterization
1.	Nuclear magnetic resonance (NMR)	Synthesis of organic dendrimer.
2.	Ultra-violet visible spectroscopy	Used to monitor the synthesis of dendrimers.
3.	Infra-red spectroscopy(IR)	To analyse the chemical transformations at the surface of dendrimers.
4.	Near infra-red spectroscopy	Used to characterize π-π stacking interaction between end groups of modified PANAM dendrimer.
5.	Fluorescence spectroscopy	To quantify defects during the synthesis of dendrimers.
6.	Raman spectroscopy	Provides relevant information about the degree of cyclodehydrogenation of polyphenylene dendrimers, characterization of PPI dendrimers.
7.	Mass spectroscopy	Characterization of small dendrimers whose mass is below 3000 Da. Electrospray ionization can be used for dendrimers that can able to form stable multicharged species.
8.	X-ray diffraction (XRD)	Determination of the chemical composition, structure, size and shape of dendrimer.
9.	Scattering techniques Small angle X-ray scattering (SAXS)	To study the arrangement of polymer segments and their segment density distribution within the molecule.
10.	Small angle neutron scattering (SANS)	To study the internal structure of the entire dendrimer.
11.	Laser light scattering (LLS)	To determine the hydrodynamic radius of dendrimers. Dynamic LLS is mainly used for the detection of aggregates.
12.	Microscopy methods Transmission microscopy	To study the morphology of dendrimers.
13.	Atomic force microscopy	For imaging study of dendrimers.
14.	Size exclusive chromatography	Separation of molecules according to their size.
15.	Electrical techniques Electron paramagnetic resonance (EPR)	Quantitative determination of the substitution efficiency on the surface of PANAM dendrimers.
16.	Electrochemistry	To study the possibility of interaction of electroactive end groups.
17.	Electrophoresis	To assess the homogeneity of several type of water soluble dendrimers.
18.	Rheology and Intrinsic viscosity	Used to determine the viscosity of dendrimers.
19.	Differential scanning calorimetry (DSC)	To detect the glass transition temperature, this depends on the molecular weight, entanglement and chain composition of polymers.
20.	Dielectric spectroscopy (DS)	Gives information about molecular dynamic processes (α-, β)
21.	Miscellaneous X-ray Photoelectronspectroscopy (XPS)	To study the chemical composition of dendrimers such as poly (aryl ether) also used for the characterization of layers.
22.	Sedimentation	Measurements of dipole moments for PMMH dendrimer.
23.	Titrimetry	To determine the number of NH_2 end groups of PAMAM dendrimers.

Ketoprofen and Diflunisal were conjugated with G_5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. PAMAM dendrimers enhanced bioavailability of indomethacin through transdermal drug delivery.

Oral drug delivery

Oral drug delivery studies using the human colon adenocarcinoma cell line have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, PGP efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter. As increase in the concentration and generation, there was and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. DNA assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics.

As a controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G_3 and G_4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construction involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5-fluorouracil. Encapsulation of 5-fluorouracil into G_4 increases in the cytotoxicity and permeation of dendrimers.

Targeted drug delivery

Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell-specific targeting agents delivered by dendrimers is folic acid PAMAM dendrimers modified with carboxy methyl PEG-5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. A third-generation dendritic unimolecular micelle with indomethacin showed a sustained *in vitro* release, as compared to cellulose membrane control. Controlled release of the flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G_4) PAMAM dendrimers. The results found that PEG-dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to un-encapsulated drug.

Gene delivery

Dendrimer-based transfection agents have become routine tools for many molecular and cell biologist's dendrimers are extensively used as non-viral vector for gene delivery. The use of dendrimers as gene transfection agents and drug-delivery devices has been extensively reviewed. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

As a solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behavior.

Cellular delivery

Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug, revealing that dendrimers can efficiently carry the complexes drug inside cells. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

Therapeutic application of dendrimers [41- 42]

Dendrimers in photodynamic therapy

The photosensitizer 5-amino levulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes. This cancer treatment involves the administration of a light-activated photosensitizing drug that selectively concentrates in diseased tissue.

Dendrimers for boron neutron capture therapy [43]

Boron neutron capture therapy (BNCT) refers to the radiation generated from the capture reaction of low-energy thermal neutrons by ^{10}B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. This radiation energy has been used successfully for the selective destruction of tissue. Dendrimers are a very fascinating compound for use as boron carriers due to their well-defined structure and multivalency.

Diagnostic applications

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 integrated molecular probe, because of their large surface area and high density of surface functionalities.

Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools in medicine, and is applicable to numerous diseases. To obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent. Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Krause and co-workers synthesized a number of potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin.

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. Wiener and coworkers developed a series of Gd(III)–DTPA-based PAMAM dendrimers. To improve the pharmacokinetic properties of dendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast agents have been considered. Synthesized a folate conjugated Gd(III)–DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

Cosmetic applications of dendrimers

Dendrimers owing to their highly branched nature have been widely used in the cosmetic industry. As they possess large number of external groups, which serves as a multifunctional properties as cosmetic agent carrier. Due to their hyper-branched nature they form a film upon deposition on a substrate and widely useful for variety of cosmetics eg. mascura and nail-polish. [44] Hydroxyl functionalized dendrimers obtained from polyester units are capable for formulating sprays, gels or lotions. Several patients have been filed for dendrimers for artificial skin tanning, hair care, skin care and nail care products.

The dendrimers possess unique properties, such as high degree of branching, multivalency, globular architecture and well-defined molecular weight makes dendrimer ideal carriers for the various applications like drug delivery, therapeutic and diagnostic agent. A large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers is one of the drug delivery to overcome problems associated with drugs. Besides these problems they also help to overcome the problem of biocompatibility and toxicity. This review clearly illustrates the various aspects of dendrimer as a novel technique for drug delivery system. A large number of drugs being developed today are facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can overcome by careful surface engineering. Dendrimers due to its superior architecture; high level of branching, multivalency, globular architecture and molecular weight, prove to be a novel and reliable method of drug delivery. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production.

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