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REVIEW ARTICLE

DENDRIMERS IN DRUG DELIVERY, DIAGNOSIS AND THERAPY: BASICS AND POTENTIAL APPLICATIONS

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ABSTRACT:

This review gives concise information about the dendrimers, properties, synthesis and application in drug delivery, diagnosis and therapy. Due to their unique architecture these have improved physical and chemical properties. They show high solubility, miscibility and reactivity due to their terminal groups. Dendrimers have well defined size, shape, molecular weight and monodispersity. These properties make the dendrimers a suitable carrier in drug delivery application. Dendrimers are unimolecular miceller in nature and due to this enhances the solubility of poorly soluble drugs. Their compatibility with DNA, heparin and polyanions make them more versatile. Dendrimers, also referred as modern day polymers, they offer much more good properties than the conventional polymers. Due to their multivalent and mono disperse character dendrimers have stimulated wide interest in the field of chemistry biology, especially in applications like drug delivery, gene therapy and chemotherapy. Self assembly produces a faster means of generating nanoscopic functional and structural systems. But their actual utility in drug delivery can be assessed only after deep understanding of factors affecting their properties and their behavior in vivo.

Key words: Dendrimers, PAMAM, monodispersity, Divergent-Convergent synthesis, carrier for drug delivery

INTRODUCTION

Dendrimers are class of well defined hyperbranched synthetic polymer systems, which can be conjugated to various chemical species, such as detection agents, imaging agents, targeting components, biomolecules, pharmaceutical/ therapeutic agents, radio ligands, affinity ligands, for various bioanalytical applications.

The term "Dendrimer" arise from two Greek words; "Dendron" meaning tree and "Meros" meaning part. A typical dendrimer structure consists of three basic components: a multi-functional central core moiety where other molecules can be trapped [1, 2], branched units that emanates from the central core and external capping-groups. The highly regular branching units are organized in layers called "generations", and represent the repeating monomer unit of these synthetic macromolecules[3]. Therefore, dendrimers can be synthesized from simple branched monomer units, in a precise and controlled fashion from trunk to branch and to leaf "surface groups".

The three-dimensional structure of dendrimers gives them a variety of unique properties, such as nanoscaled globular shape, well-defined functional groups at the periphery, hydrophobic or hydrophilic cavities in the interior and extremely low polydispersity [4], and thus a wide range of potential applications.

Dendrimer is a nanoparticle and so has advantages over microparticles or others due to its small size, easy uptake by cells (through endocytosis) [4, 5]. They are branched macromolecules have a central core unit having a high degree of molecular uniformity, narrow molecular weight, distribution, specific size and shape characteristics, and a highly- functionalized, terminal surface. The manufacturing process is a series of repetitive steps generating shells, starting with a central initiator core. Each subsequent shell represents a new "generation" of polymer with a larger molecular diameter, twice the number of reactive surface sites, and approximately double the molecular weight of the preceding generation. Dendrimers have cellular uptake through endocytosis and thus brings drug "bound" to dendrimers into the cell.

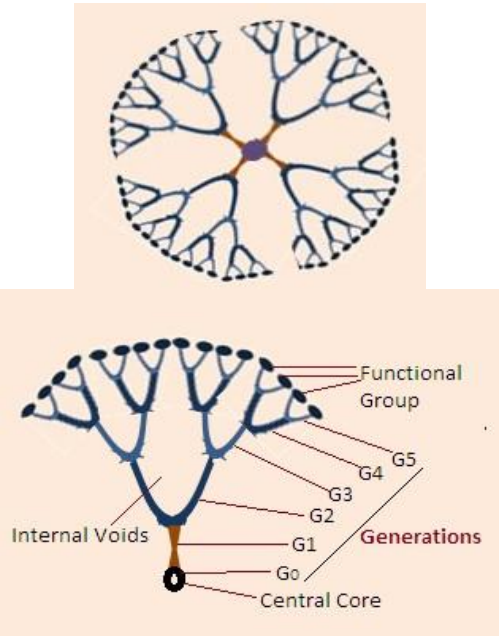

Figure 1: Schematic representation of the Dendrimer Structure

The precise control over the distribution of drugs is highly valuable to abolish the typical drawbacks of traditional medicine. In recent years, improved pharmacokinetics, biodistribution and controlled release of the drug to the specific targeted site has been achieved with polymer based drug delivery[6] Unlike traditional polymers, dendrimers have received considerable attention in biological applications due to their high water solubility,[7] biocompatibility,[8] polyvalency[9] and precise molecular weight.[3] These features make them an ideal carrier for drug delivery and targeting applications. For investigating dendrimers as drug delivery vehicles, their biopermeability across the biological membranes should be considered.

In this review, we report on the noteworthy scientific advances and most recent literature, dealing with the properties, their advantage over conventional linear polymers and their application in drug delivery, diagnosis and therapy.

Table 1: Various Dendrimer based products

Name of Product	Type	Company	Use	Status	Ref
Vivagel	Poly-L-lysine	Starpharma	Prevention of HIV infection	Clinical trials (Phase 3)	9
Priostar	PEHAM/PEA	Starpharma	Targeted diagnostic and therapeutic delivery for cancer	Marketed	10, 11
Starburst	PAMAM	Dow chemical	Targeted diagnostic and therapeutic delivery for cancer	Marketed	12
Stratus CS	PAMAM	Dade Behring	Cardiac marker	Marketed	13
Astramol®	PPI	Starpharma	-	Marketed	14
Taxotere	ND	Sanofi Aventis	Anticancer drug delivery	-	-
SuperFect	PAMAM	Qiagen	Gene transfection	Marketed	15,16
Alert ticket	PAMAM	US Army Research Lab.	Anthrax detection	Marketed	17
Dendrimer-docetaxel	ND	Starpharma	Breast cancer treatment	Preclinical	18
Dendrimer-oxaliplatin	ND	Starpharma	Colon cancer treatment	Preclinical	18

ND: not define, PEHAM: Poly (etherhydroxylamine), PEA: Poly (esteramine), PAMAM: Polyamidoamine, PPI: Poly (propylene imine), HIV: Human immunodeficiency virus, STDs: Sexually transmitted diseases

WHAT MAKES DENDRIMERS SPECIAL IN DRUG DELIVERY

Dendrimers are dentritic polymers that have very well-defined nanostructures and high level control over its size, branching density and surface functionality. They are useful nanoscale carriers for drug and gene delivery. Both hydrophilic and phrophobic drug molecules can be formulated with dendrimers. They have been applied in intravenous, oral, pulmonary, nasal, ocular, and transdermal drug delivery systems.

Dendrimers have shown enormous potential as nanocarrier/delivery systems because they can cross cell barriers by both paracellular and transcellular pathways. The ability to statistically modify and optimize the number and/or ratio of dendrimer surface groups that influence biodistribution, receptor-mediated targeting, therapy dosage or controlled release of drugs from the dendrimer interior.

The three-dimensional structure of dendrimers gives them a variety of unique properties, such as nanoscaled globular shape, well-defined functional groups at the periphery, hydrophobic or hydrophilic cavities in the interior and extremely low polydispersity [19], and thus a wide range of potential applications. For example, most dendrimers have globular structures with molecular diameters less than 10 nm, which can be modulated by varying dendrimer generations.

This property gives dendrimers similar sizes and shapes as specific proteins and other biomolecules and thereby makes them perfect as biomimics [20]. Also, the highly regular branching pattern of dendrimers imbues these dendritic architectures with well-defined numbers of periphery functional groups, providing opportunities for the presence

of drug molecules, targeting moieties, and solubilizing groups on the surface in a multivalent fashion [21, 22]. Moreover, hydrophobic and hydrophilic cavities in the interior of dendrimers make them useful candidates as unimolecular micelles for the encapsulation of guest molecules, especially drugs [23–24]. Finally, the low polydispersity of dendrimers assures the reproducibility of biodistribution of polymeric prodrugs using them as scaffolds [25, 26].

Nanoparticles having a size in the range 1–10 nm have the capacity to diffuse into tumor cells. This helps to overcome limitations relating to chemotherapy using free drug such as poor in vivo/in vitro correlation and overcome other possible resistances offered by tumors.

Dendrimers are one of the most useful non-viral gene delivery systems. Their ability to transfect cells without inducing toxicity and be tuned for stimuli-induced gene delivery confers a great advantage over other gene delivery vectors for use in vivo.

The well-defined hyperbranched structure of dendrimers has motivated chemists to explore the possibility for mimicking protein functions with dendritic macromolecules, such as O2-carrying haemoproteins and coenzyme B12. Thus, dendrimers can be tuned for: (i) be stimuli-responsive nanocarriers, (ii) include moleculartags, (iii) possess high payload efficiency, (iv) decrease dosage requirements as well as re-dosage frequency and (v) target delivery and minimize drug migration, thus suppressing secondary effects during drug treatment.

The interesting nanoscale architecture of dendrimers confers several structural benefits over linear polymers, larger nanoparticles and liposomes. Such advantages include rapid cellular entry, reduced macrophage uptake, targetability and more facile passage across biological barriers by transcytosis[27]. In comparison to linear polymers, dendrimers are multivalent owing to the presence of high multiplicities of reactive surface end groups, making them ideal drug carriers with higher drug payload capacities[28]. Encapsulation of drugs in PEGylated dendrimers can lead to enhanced permeation and retention (EPR) of the drug.

To briefly reiterate, properties of dendritic polymers important for drug delivery include negligible polydispersity, a high-density payload of pro-drug, and the ability to selectively release the active form of drug precisely at its intended site of action. Therefore, detailed in vivo toxicity examination of dendrimers is important and can facilitate the design of tailored dendrimer-mediated CNS drug-delivery systems.

They can be synthesized and designed for specific applications. Due to their feasible topology, functionality and dimensions, they are ideal drug delivery systems; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.[29-30]

The covalent attachment of drugs to the surface groups of dendrimers through hydrolysable or biodegradable linkages enhances the pharmacological properties of the drug and offers the opportunity for a greater control over drug release.

ADVANTAGES OF DENDRIMERS

The following properties of the dendrimers make them as an ideal carrier for drug delivery, therapy and diagnosis.

1. *Low polydispersity index:*

They have lower polydispersity index, due to stringent control during synthesis. 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 most of the space remains hollow towards core. This region can be utilized for entrapment of variety of drugs[29]

2. *Enhanced permeability and retention effect*

Size of dendrimers i.e. (Generation 4-4.4 nm) is in nano range. Cancer cells have leaky membranes and having higher biopermeability for anticancer drugs. Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectively than small molecules. Lymphatic system is one way and drug loaded dendrimers may get retained inside [31].

3. *High permeability*

This property improves intracellular trafficking of drugs. Dendrimers can cross biobarriers like blood brain barrier, cell membrane. Nanometre range and uniformity in size enhance their ability to cross cell membranes and diminishes the risk of undesired clearance from the body through the liver or spleen [32-33].

4. *Sustained /extended effect*

Dendrimers releases drug in a sustained manner. PAMAM dendrimers exhibited slower release, higher accumulation in solid tumors, and lower toxicity. Conjugation with Polyethylene glycol on the surface of these nanocarriers avoids non-specific interaction with plasma proteins or engulfment. Increase in blood circulation time is essential to achieve desired clinical effect [34].

5. *Higher Solublization Potential*

Ionic interaction, hydrogen bonding and hydrophobic interactions are probable mechanism by which dendrimers show its solubility enhancing property. Most anticancer drugs have poor solubility and can be loaded into dendrimers to improve solubility [35-36]. Dendrimers are capable of improving 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.

6. *High uniformity and purity*

The synthetic process used produces dendrimers with uniform sizes range, well defined surface functionality, and negligible impurity. Monodispersed dendrimers would facilitate us to attain targeted drug delivery [37, 38].

7. *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. The surface modification may allow designing dendrimers mimicking biological exo-receptors, substrates, inhibitors or cofactors. Free surface groups can form complex or conjugates with drug excellent molecules or ligands by

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using cross linking agents. The surface of dendrimers may be conjugated with ligands, solubility modifiers, and stealth molecules [21,39].

8. *High loading capacity*

Dendrimers structures can be used to load and store a wide range of organic or inorganic molecules by encapsulation and absorption on surface. Drug can get entrapped inside the internal cavities as well as electro statically in the surface of dendrimers [40].

9. *High stability*

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

10. *Low toxicity*

Most dendrimers systems display very low cytotoxicity levels but have good biodegradability [24]. PEGylation of the dendrimer surface can prolong its circulation time and reduce its toxicity

11. *Low immunogenicity*

Dendrimers shows low or negligible immunogenic response when injected or used topically [41]. The problems in vesicular system like chemical instability, drug leakage, aggregation and fusion during storage, solubility in physiological environment, lysis of phospholipids, purity of natural phospholipids lack in dendritic system

12. Dendrimers can be modified as stimuli responsive to release drug. The similarity of dendrimers structure with IgM antibodies (pentamers radially distributed) suggest that they may be used to function as antibodies e.g. activation of macrophages, recognition, and high affinity to antigen.

MAJOR CHALLENGES AND WAYS TO OVERCOME

Despite these promising results, this field is still in its infancy. It is known that the dendrimers may have toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity.

1. *Toxicity*

A basic issue in drug delivery is the avoidance of non-specific, systemic, or off target toxicity. Appropriate modifications of the dendrimers surface can greatly reduce their toxicity.[42] Such modified dendrimers can be used in nanomedical applications, as they possess the advantage of dendrimers spatial structure and simultaneously possess reduced toxic activity. Therefore, PAMAM dendrimers are more cationic than anionic cytotoxic. An example of interaction with lipid bilayers of cells occurs with the cationic dendrimer-G7 PAMAM which comes to form holes 15-40 nm in diameter, which disturbs the flow of electrolyte causing cell death.

To overcome the problem of toxicity the group of Michal Ciolkowski and Johannes F. Petersen has done surface modification of polyamidoamine (PAMAM) dendrimer of the fourth generation (G4). The amine surface groups of a G4 PAMAM-NH2 dendrimer were transformed into pyrrolidone derivatives by means of reaction with dimethyl itaconate. The researchers reported reduced toxicity through interaction studies with human serum albumin (HSA), influence on viability of mouse neuroblastoma (N2a) cell line, as well as through hemolytic activity.[43]

PEGylation of the dendrimer surface can prolong its circulation time and reduce its toxicity. BBB- or CNS-targeting ligand modification of the dendrimer surface can improve the rate and duration of drug delivery to brain tumor cells prior to the clearance of the remaining drug-delivery system. Imaging and diagnostic agents incorporated into dendrimers can help with the evaluation of brain tumors and dendrimer-associated CNS toxicity. However, challenges still exist regarding the deeper toxicological studies, specific targeting, and noninvasive alternative drug administration methods. The ultimate goal of dendrimer-mediated CNS drug-delivery systems is to engineer the dendrimers to be safe and to enable their longterm use without the accumulation of adverse effects.

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. The pegylated dendrimers have lower cytotoxicity and longer stay in the blood than non-pegylated dendrimers. PEGylation increases the physical dendrimers size which reduces renal clearance[44-45]

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2. *Water Solubility and Immunogenicity*

There are two biocompatibility issues presents in dendrimers, namely water solubility and immunogenicity, are closely related insofar as highly-hydrated macromolecules tend to be less immunogenic. With dendrimers, there are many options available to overcome difficulties that arise in these areas. For example, solubility can be readily adjusted by surface modifications to surface chemistry or by the addition of conjugated ligands. Moreover, dendrimers such as the commonly used G3, G5, and G7 PAMAM clusters are not inherently immunogenic [46]. Derivatized PAMAM such as the G4D-(1B4M-Gd)62 magnetic resonance imaging (MRI) contrast dendrimer, however, can become immunogenic (which is not surprising considering the deliberate efforts to render small molecules immunogenic through presentation on a dendritic scaffold). This problem once again tying together the concepts of solubility and immunity – was overcome in one study by conjugation of poly(ethylene glycol) (PEG) to the surface of the dendrimer. Notably, PEG also had the positive effect of decreasing non-specific clearance from the blood, likely due to the increased hydration and resulting solubility of the particle [47].

PROPERTIES OF DENDRIMERS

1. *Monodispersivity, size and shape*

The monodispersion means that the dendrimers has a well defined molecular structure and without large individual variations, in other 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 [57]. Such control facilitates the research, because it becomes a tool with defined size ranges [58]. The advantage of low polydispersity makes it possible to predict the pharmacokinetic behavior of dendrimers because little variation of molecules weight makes it possible to know the sample movements of these polymers for biological organism [59]. 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 higher generation shows compact-spherical shape [60].

Due to their nanometric scales and other properties that are similar to proteins, dendrimers are also known as artificial proteins and gain attention in studies that make use of their biomimetic properties. The dendrimer can be controlled by molecular engineering so that its size resembling to antibodies, enzymes and globular proteins[61-63].

2. *Polivalency*

Polyvalency is useful as it provides for versatile functionalization; it is also extremely important to 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 [64]. Areas of high multivalent dendrimers of generations can contain a large number of functional groups. This makes the surface of the dendrimer branches and more susceptible to interactions with a large number of species. The multivalencyallows better interaction with biological targets since most of the molecular interactions occur through biological multivalent bonds. The valency binder is the number of links that can be established with a receiver or receivers. The strength of multivalent interactions exceeds the sum of the forces. Dendrimers as potential platform in nanotechnology-based drug delivery systems exhibit higher biological activity compared to conventional drug molecules because the dendrimer can react with multiple receivers at once in the biological site of action [65].

3. *Solubility and biocompability*

Surface groups of the dendrimers play an important role in the solubility of dendrimers. Dendrimers generally have greater solubility in common solvents as compared to linear polymers. However, the solubility depends on various components in addition to the surface groups as the generation number, nature of repeating units and even the core. What enables the construction of dendrimers perfectly soluble in a large number of solvents, ensuring both the solubility of dendrimers in organic solvents, which leads a rapid dissolution in water and enhances the activity of hydrophobic molecules [62].

If the surface end groups are hydrophobic in nature, then dendrimers are soluble in nonpolar solvent. If the surface end groups are hydrophilic in nature and dendrimers are soluble in polar solvent. The high solubility, miscibility and reactivity and binding capacity of dendrimers is due to the presence of many chain end groups [60,66,67]. PAMAM dendrimers have received considerable attention because its ability to solubilize water-insoluble drugs and transporting them through the biomembranes, increasing the bioavailability of these drugs [68, 69].

Before being used as biological agents in drug delivery, dendrimers should meet a variety of requirements such as: (1) having no toxicity, (2) is not immunogenic (3) ability to cross biological barriers such as the walls and the intestinal membranes, (4) remain in circulation long enough to be effective clinically (5) ability to deliver specific structures [70, 71]. The biological properties as, for example, immunogenicity and toxicity depends mainly on the size and the surface groups of the dendrimers. The interior structure therefore has less influence because usually the dendrimer interactions occur with the outside via the exposed surface groups, which makes the dendrimers able to cross cell surfaces.

4. *Toxicity*

It is known that the dendrimers may cause toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity. Therefore, PAMAM dendrimers are more cationic than anionic cytotoxic. An example of interaction with lipid bilayers of cells occurs with the cationic dendrimer-G7 PAMAM which comes to form holes 15-40 nm in diameter, which disturbs the flow of electrolyte causing cell death [72]. 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. The pegylated dendrimers have lower cytotoxicity and longer stay in the blood than non-pegylated dendrimers. PEGylation increases the physical dendrimers size which reduces renal clearance since the glomerular filtration limit is reached [73, 74].

5. *Interactions of drugs with dendrimers*

The dendrimers designed for drug delivery have the intention to improve the pharmacokinetics and biodistribution of drugs and may also provide a controlled release of the drug with the goal of reaching the target tissues [75]. The strategy of coupling small molecules to polymeric scaffolds by covalent linkages to improve their pharmacological properties has been under experimental test for over three decades [76, 21]. 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.

Dendrimers interact with drug molecules physically by absorption 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 dendrimer [15,77,78]. The technique of drugs encapsulation may be a purely physical entrapment or involve interactions with specific structures within the dendrimer [79]. Encapsulation is a general strategy for low molecular

weight molecules and are transported on the bioactive surface of dendrimers induce undesired immunogenicity [63].

Molecular recognition events at dendrimer surfaces are distinguished by the large number of often identical end groups presented by the dendritic host. When these groups are charged, the surface may have as a polyelectrolyte and is likely to electrostatically attract oppositely charged molecules [80]. One example of electrostatic interactions between polyelectrolyte dendrimers and charged species include the aggregation of methylene blue on the dendrimer surface and the binding of EPR probes such as copper complexes and nitroxide cation radicals [81].

The empty internal cavities generally have hydrophobic properties which allow interactions with poorly soluble drugs. The existence of atoms of nitrogen and oxygen in the internal structure of the dendrimer allows interaction by hydrogen bonds with the drug [62]. The high density of functional groups are ionizable at the periphery of the dendrimer (such as amines and carboxyl groups) permits to fix a large number of ionizable drugs by electrostatic interactions and transporting them to their destination. Covalent interaction method offers advantages over previous methods, therefore allow multiple drugs to be attached to each dendrimer through the numerous groups of the surface, the covalent bonds between the drug and the polymer are likely more difficult to break giving them greater control over the drugs, overcoming the force of interaction achieved by electrostatic bonds and encapsulation [75].

6. *Viscosity*

In solution dendrimers form a tightly packed ball which influences its rheological properties. The intrinsic viscosity dendrimers solution does not exhibit linear relationship with mass but it is highest for a specific generation and then it begins to decrease.

7. *Self-assembling dendrimers*.

Another fascinating and rapidly developing area of chemistry is that of self-assembly. Self-assembly is the spontaneous, precise association of chemical species by specific, complementary intermolecular forces. Recently, the selfassembly of dendritic structures has been of increasing interest [82]. Because dendrimers contain three distinct structural parts (the core, end-groups, and branched units connecting the core and periphery), there are three strategies for self-assembling dendrimers. The first is to create Dendrons with a core unit that is capable of recognizing itself or a ditopic or polytopic core structure, therefore leading to spontaneous formation of a dendrimer [83]. A self-assembling dendrimer using pseudorotaxane formation as the organizing force was reported by Gibson and coworkers [84].

FACTORS AFFECTING DENDRIMER PROPERTIES

1. *Effect of pH*

The study of structural behaviour of PAMAM dendrimers as a function of pH, by applying molecular dynamics show that the dendrimer has an extended conformation, based on a highly ordered structure at low pH (pH<4). 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 consequence of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. At higher pH (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[85,86].

2. *Effect of Solvent*

The solvation power of any solvent to solvate the dendrimer is a very important parameter when investigating the conformational state of a dendrimer. Dendrimers of all generations generally exhibit a larger extent of back-folding with decreasing solvent quality, *i.e*. decreasing solvation. 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 concluded that a nonpolar solvent like benzene, poorly solvates the dendrimers favouring intramolecular interactions between the dendrimer segments and back-folding. But, a 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 solvents solvate the dendrimer arms and induce a higher molecular density on the dendrimer surface. Backfolding 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 [66].

3. *Effect of Salt*

High ionic strength (high concentration of salts) has a strong effect on charged PPI dendrimers and favours a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor solvation. At low salt conditions, the repulsive forces between the charged dendrimer segments results in an extended conformation in order to minimize charge repulsion in the structure[85].

4. *Effect of Concentration*

In 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 affect 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.

SYNTHESIS OF DENDRIMERS:

1. *Convergent methodology*

This was pioneered by Hawker and Frechet in 1990's. This strategy refers to the inward growth by gradually assembling surface units with reactive monomers. The deactive side products produced during reactions gets easily separated by purification, but this becomes harder in higher generations due to similarity in products and reactants. The convergent methodology suffers from one major limitation that it gives low yield in the synthesis of large structures and hence is suitable for production of only lower generation dendrimers.[19, 87]

2. *Divergent Method*

Divergent Method involves the coupling of monomeric molecules that possesses reactive and protective groups with the multifunctional core moiety which leads to stepwise addition of generations around the core followed by removal of protecting groups. PAMAM-NH2 dendrimers were firstly synthesized by coupling N-(2-aminoethyl) acryl amide monomers to an ammonia core and today they are the most systematically synthesized and commercialized family of dendrimers using this methodology. This method offers an advantage of producing modified dendrimers by changing the end groups and in turn their physicochemical properties can be altered as per the required application. Although, this approach suffers from limitation of structural defects due to incomplete reaction of groups which can be trounced by the excessive addition of monomeric units.[88,89]

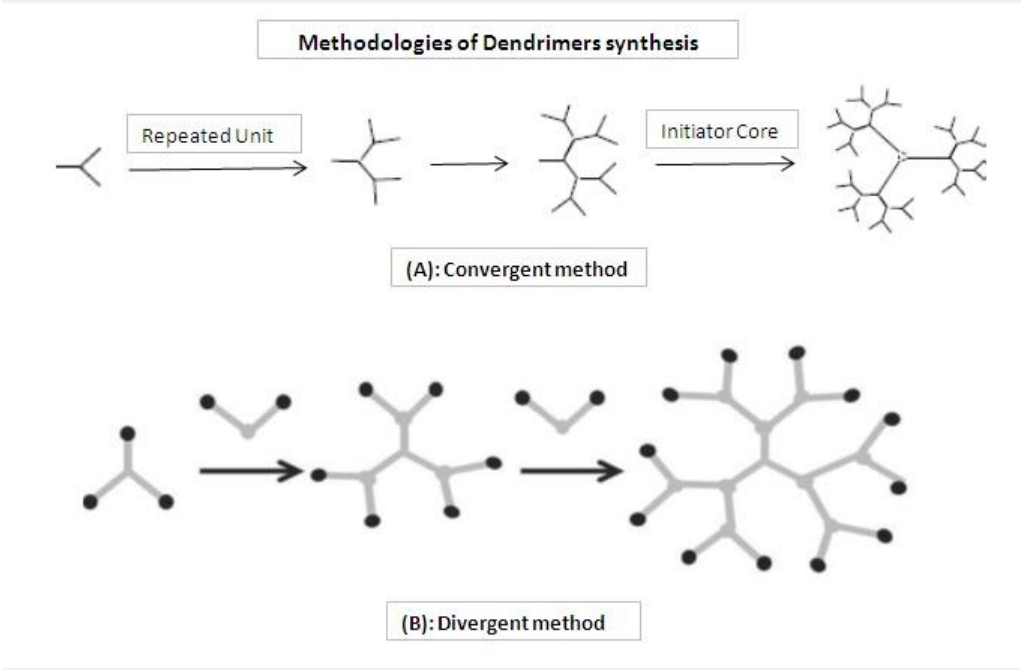

Figure 2: Synthesis approaches of dendrimers (A) Convergent method (B) Divergent method

3. *Double Exponential and Mixed Growth*

In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps.[87,90]

4. *Hypercores and Branched Monomers growth*

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields.

MECHANISMSOF DRUG DELIVERY:

Dendrimers are particularly attractive as they offer a high drug-loading capacity. Due to the well defined 3D structure and many surface functional groups, drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure or by interacting with drugs at their terminal functional groups via electrostatic or covalent bonds forming prodrug. Encapsulation of drugs and dendrimer-drug conjugates [91-92] are two main methods of dendrimer drug delivery.

1. *Non-covalent Encapsulation of Drugs / Host –Guest Relation*

Incorporation of small organic molecules may be a result of non-bonding interactions with specific groups within dendrimer, i.e. just physical entrapment

Encapsulation of drugs uses the satiric bulk of the exterior of the dendrimer or Interactions between the dendrimer and drug to trap the drug inside the dendrimer. Such a system can be used to encapsulate drugs and provide controlled delivery. Initial studies of dendrimer as potential delivery systems focused on their use as unimolecular micelles and 'dendritic boxes' for the noncovalent encapsulation of drug molecules. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications, and hydrophobic drugs and dye molecules

were incorporated into various dendrimer cores. An advantage of using dendritic unimolecular micelles rather than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected[93].

Dendrimers can be used as dendritic boxes and unimolecular micelles (dendrimer‐drug networks) for the incorporation of hydrophobic/hydrophilic molecules by host guest interactions inside their empty cavities (nanoscale containers) present around core.[94,95] Jansen et al. were the first to entrap the rose bengal dye molecules in PPI dendrimers by using tert‐butyloxycarbonyl (t‐Boc) groups and led to the production of stable dendritic box that possess the bulky amino groups on the dendrimer surface.[96]

The dendritic unimolecular micelles contain the hydrophobic cores surrounded by hydrophilic shells and they offer an advantage over conventional polymeric micelles such that the micellar structure is maintained at all the concentrations because the hydrophobic segments are covalently connected.

2. Covalent Dendrimer–Drug Conjugates

Alternatively, the exploitation of well‐defined multivalent aspect of dendrimers allows the attachment of drug molecules to its periphery that result in complex formation. The resultant complexes are formed either due to the electrostatic interactions between the drug and dendrimer or conjugation of the drug to dendrimer molecule. Through electrostatic interactions, various ionizable drugs form complexes with the large number of ionizable terminal surface groups of dendrimers.[97]

In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids .The drug loading can be tuned by varying the generation number of the dendrimer, and release of the drug can be controlled by incorporating degradable linkages between the drug and dendrimer.

Moreover, the drugs can be covalently conjugated to dendrimers through some spacers that may include PEG, p‐amino benzoic acid, p‐amino hippuric acid and lauryl chains etc., or biodegradable linkages such as amide or ester bonds. This prodrug approach has been found to increase the stability of drugs and has affected their release kinetics significantly. Several researchers have successfully conjugated naproxen,[98] propranolol[92] with PAMAM dendrimers. The results have shown the enhanced solubility and controlled release of drugs from these complexes in comparison to the pure drug. Apart from these, many anticancer drugs have also been conjugated and used for drug targeting. For example, epirubicin prodrug was developed by conjugating it with PEG dendrimers containing aminoadipic acid as branching molecules. These conjugates exhibited increased blood residence time and showed improved therapeutic action. The study revealed that PEG dendrimers increased the stability of bound drug toward chemical degradation and hence can be used potentially in the development of prodrugs of large molecules.[99]

Conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with non-specific toxicity and poor water solubility show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors. Furthermore, the dendrimer–platinum complex has been found to show increased efficacy relative to cisplatin in the treatment of subcutaneous B16F10 melanoma. By using a careful synthetic strategy with two different chain end functionalities, it is also possible to attach both hydrophobic model drugs and PEO moieties to the dendrimer periphery in a controlled manner. Aliphatic polyester dendrimers based on 2,2-bis(hyroxymethyl)propionic acid are promising dendrimer backbones for the development of anticancer drug conjugates[100].

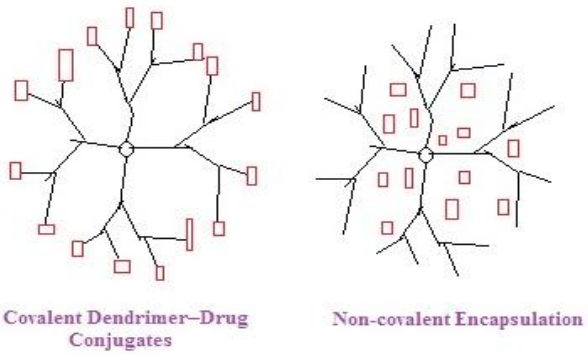

Figure 3: Different types of drug‐dendrimer interactions.

APPLICATION OF DENDRIMERS IN DRUG DELIVERY

Over the past 30 years greater attention has been focused on development of controlled and sustained drug delivery systems. Amongst the extensive research has been carried in designing of polymeric drug delivery systems[101].

The development of dendrimer based efficient drug delivery systems has attracted a great deal of attention over the last few years. Unlike traditional polymers, dendrimers can be obtained in precise molecular weights even at high generations, which as previously highlighted can provide a reproducible pharmacokinetic behavior. This feature makes them ideal candidates for drug delivery applications.

However, efficient drug delivery systems should meet other criteria, such as: (i) structural control over the size and shape of drug or imaging-agent cargo-space; (ii) biocompatibility, non-toxic polymer/pendant functionality; (iii) precise, nanoscale-container and/or scaffolding properties with high drug-loading capacity; (iv) well-defined scaffolding and/or surface modifiable functionality for cell specific targeting moieties; (v) lack of immunogenicity; (vi) appropriate cellular adhesion and internalization, (vii) adequate bio-elimination or biodegradation; (viii) controlled or stimuli-responsive drug release features; (ix) molecular level isolation and protection of the drug against inactivation during transit to target cells; (x) minimal non-specific cellular and blood–protein binding properties; (xi) ease of consistent, reproducible, clinical grade synthesis.

1. Dendrimers in CNS Drug Delivery

As the vast majority of potential CNS compounds have limited brain uptake, they may benefit from the use of advanced delivery systems in order to cross the BBB. The drug is encapsulated in, or associated to the particle, thereby masking its physiochemical characteristics[102].

Nanomedicine has shown great potential for the treatment of many CNS diseases. Nanomedicine is the biomedical and pharmaceutical application of nanotechnology for making nanocarriers of therapeutics and imaging agents, nanoelectronic biosensors, and nanodevices with nanostructures. A number of nanocarrier delivery systems, including dendrimers, liposomes, polymeric micelles, linear polymers, quantum dots, and iron oxide Nanoparticles have been developed and have demonstrated promising properties in CNS drug deliver[103]. Among these, much attention has been paid to dendrimers because of their advantages, which include (1) the ability to maintain drug levels in a therapeutically desirable range, (2) increased half-life, (3) increased solubility, stability, and permeability of drugs, (4) the capability to deliver a variety of drugs, (5) reduced macrophage uptake, (6) targeting ability, (7) facile passage across biological barriers by transcytosis, (8) rapid cellular entry, (9) improved delivery efficiency, and (10) reduced side effects by targeted delivery.[27, 104, 105]

Polyesters based dendrimers have been proposed for CNS regenerative medicine. Dhanikula et al. [106, 107] suggested the use of polyether-copolyester (PEPE) dendrimers conjugated with d-glucosamine, and loaded with methotrexate (MTX) in order to allow a better delivery across the BBB. The results revealed that the efficacy of MTX-loaded dendrimers was established against U87 MG and U 343 MGa cells (two glioma cell lines). In vitro studies revealed that glucosylated dendrimers were internalized by endocytosis in significantly higher amounts than non-glucosylated dendrimers by both the cell lines. Moreover, the amount of MTX-transported across an in vitro model of the BBB was three to five times more after loading in the dendrimers, which indicates that glucosylation further increased the cumulative permeation of dendrimers across BBB, and hence increased the amount of MTX available across it. This work evaluated a different set of dendrimers, as well as different strategy, for potential use delivery across the BBB. However, it should be considered with caution, as only in vitro models were used, and the in vivo proof of concept is yet to be demonstrated.

Prieto et al. [108] investigated the cytotoxicity of sulfadiazine complexed with fourth-generation PAMAM dendrimers. Cell culture studies using fibroblasts (Vero cells) and macrophages (J-774 cells) revealed that the dendrimeric sulfadiazine complexes did not affect membrane integrity at low concentrations (0.03!M). Moreover, cytotoxicity tests using human intestinal adenocarcinoma cell line (Caco-2 cells) showed that dendrimeric sulfadiazine did not reduce viability of Caco-2 cells over the tested concentrations as compared to that for PAMAM(G4). Remarkably, the in vivo study has shown that brain and muscle of Wistar rats are the main targets of intravenous administration of dendrimeric sulfadiazine, which can be advantageous for drug delivery applications directed to central nervous system.

2. Dendrimers in Oral Drug Delivery

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance.[109]

Dendrimers are suitable candidate in oral drug delivery because dendrimers loosened the tight junctions of epithelial layer and thus an improvement in the absorption of small molecular weight drugs was achieved [110]. The transepithelial transport and toxicity of polyamidoamine dendrimers as carriers for oral drug delivery has been reviewed by Sadekar and Ghandehari [111]

Kolhe et al. [112] demonstrated that ibuprofen predominantly forms a complex with PAMAM (G3 and G4) dendrimers because of the ionic interaction between the –NH2 end groups and the carboxyl group of ibuprofen. In this work, they demonstrated that the in vitro release of ibuprofen from drug–dendrimer complex is appreciably slower compared to pure ibuprofen. Moreover, the FITC-labeled dendrimer-complexed drug enters human lung epithelial carcinoma A549 cells much faster than pure drug, suggesting that dendrimers may be able to carry the complexed drug inside cells efficiently.

In another work Kolhe et al [21] synthesized a fourth-generation PAMAM (PAMAM-OH) dendrimer covalently linked to ibuprofen using dicyclohexylcarbodiimide (DCC) as a coupling agent. A high payload nanocarrier was obtained; [113] molecules of ibuprofen were covalently conjugated to one molecule of PAMAM-OH (G4) dendrimer. FITC-labeled dendrimer–drug conjugate nanoparticles internalization was evaluated in vitro once using A549 cells. The pharmacological activity of the dendrimer–ibuprofen conjugate was compared to pure ibuprofen at various time points by measuring the suppression of prostaglandin E2. Results demonstrated the high internalization efficiency of the FITC-labeled dendrimer–drug conjugate and superior therapeutic activity due to faster prostaglandin E2 suppression. Thus, the results suggest that the dendrimer–ibuprofen conjugate improve the drug efficacy by enhanced cellular delivery, and may produce a rapid pharmacological response.

3. Dendrimers in Nasal Drug Delivery

Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of pre-systemic elimination of gastro intestinal tract and depending on the particular drug.[114] Nasal administration offers an interesting alternative for achieving systemic drug effects to the parenteral route, which can be inconvenient or oral administration, which can result in unacceptably low bioavailabilities.[115]

Polyamidoamine (PAMAM) dendrimer has draws attention for nose-to-brain targeting. These dendrimers are repetitive branches that grow from a core. Many versatile molecules can be attached to their surface. Kim et al. connected an arginine onto the surface of a PAMAM dendrimer [116]. This resulted in nanoparticles with a size of 188.7 ± 1.9 nm and a charge of +22.3 mV. Small interference RNA (siRNA) targeting against the high mobility group box 1 protein (HMGB1) was electrostatically attached onto the nanoparticles. HMGB1 is released by dying cells and acts as a danger signal, thereby aggravating the damage of a stroke or other neurotoxic insults. Upon intranasal administration, they observed a wide distribution of the construct into the brain, including the hypothalamus, the amygdala, the cerebral cortex, and the striatum. Moreover, the localization of the PAMAM dendrimer and the siRNA was associated with an efficient knock-down of the protein of interest: HMGB1. When a stroke was induced into animals, the group that received the intranasal

administration of the construct had a remarkably decreased infarction volume.

The potential of mucoadhesive gel of dendrimers formulations for nose to brain delivery was also displayed by Perez et al. [117]. They coupled radioactive siRNA to PAMAM dendrimers to form dendriplexes, and formulated these particles into mucoadhesive gels containing either 1% (w/w) chitosan or 0.25% (w/w) carbopol 974P NFTM. These gels were prepared by blending the chitosan or carbopol with 23% (w/w) of thermosensible poloxamer to obtain in-situ gelation. Such a thermosetting gel has a phase transition below the temperature in the nasal cavity (32 °C to 35 °C) and above room temperature. Therefore it can be administered as a liquid. Different concentrations of the different gels were tested and no toxicity was observed. Two intranasal doses were necessary to achieve higher brain concentrations of radioactivity than achieved by intravenous administration of dendriplexes or intranasal administration of naked siRNA.

4. Dendrimers in Gene Delivery

The ability to transfer genetic material efficiently, into the nucleus and cytoplasm of eukaryotic cells may allow treatment of a variety of genetic disorders. There are so many vectors and physical methods are reported for in vivo Gene delivery.

Commonly two approaches viz. viral and non‑viral based are being used to facilitate the gene delivery to target cells. Although viral carriers (Synthetic DNA delivery systems) can achieve rapid transfection, but low efficiency, immunological and oncologic adverse effects associated with these vectors has remained a topic of concern[118-120].

Non‑viral gene delivery vectors offer the usage of natural/synthetic molecules or physical forces to transfer genetic material to targeted cells. Several advantages such as ease of fabrication, targeting ability, potential for repeat administration and low immune response have led to the usage of non‑viral vectors preferably for gene therapy.

Dendrimers are one of the most useful non-viral gene delivery systems and play a significant role in the development of non-viral vectors for gene delivery due to their ability to transfect cells without inducing toxicity, the high charge density and tunable surface functional groups, thus allowing optimal condensation and formation of nanostructures with DNA, the so-called “dendriplexes”.

Many factors affect the efficiency of non-viral gene delivery systems. For successful gene therapy the genetic material should be permanently integrated and expressed by cells. In this context, Galetti et al.[121] demonstrated that antisense oligonucleotides (ONs, gene-specific sequences of nucleic acids with 15–25 bases) directed to LMP1 mRNA, effectively suppressed LMP1 gene expression, which plays a key role for growth transformation and immortalization of B lymphocytes. The efficiency of three cationic carriers on the delivery of anti-LMP1-ON to their site of action in Epstein Barr virus (EBV)-infected B lymphocytes was investigated. Results showed that liposomes, dendrimers or transferrin-PLL-conjugated ON were internalized by the cells at an extent several fold higher than that of the naked oligomers. Using Superfect®, a dendrimeric polycation with terminal amine groups, a higher intracellular concentration of ON was obtained as observed by both cytofluorimetric and confocal microscopy analyses. However, there was some evidence of toxicity induced by the positively charged dendrimers on the lymphocytes’ membranes, and the lack of intracellular mRNA-ON duplex formation and of LMP1 mRNA degradation indicated a failure of this carrier.

Among various commercially available dendrimers, PAMAM dendrimers have received the most attention as potential non‑viral gene delivery agents due to their cationic nature which enables deoxyribonucleic acid (DNA) binding at physiological pH.[122]

Pandita et al. prepared dendrimer based gene delivery vectors taking advantage of the cationic nature and the “proton‑sponge” effect of these dendrimers. Arginine‑glycine‑aspartic (RGD) nanoclusters were formed by conjugation of G5 and G6 PAMAM dendrimers with a varying number of peptides containing the RGD motif, in view of its targeting capabilities. Authors reported that the system wherein G6 PAMAM dendrimer was conjugated to eight peptide arms enhanced the gene expression in mesenchymal stem cells and presented a 2‑fold higher bone morphogenetic protein‑2 expression in comparison to the G6 native dendrimer.[123] Various published literature suggests that functionalized dendrimers are much less toxic than the native dendrimers. Same group synthesized a new family of gene delivery vectors consisting of G5 PAMAM dendrimer core randomly linked to hydrophobic chains (with varying chain length and numbers). In vitro studies revealed a remarkable capacity of these vectors for internalizing pDNA with very low levels of cytotoxicity, being this effect positively correlated with the CH2 content present in the hydrophobic moiety. The results demonstrated that vectors containing the smallest hydrophobic chains showed the higher gene expression efficiency.[124] Further, functionalized PAMAM dendrimers exhibited low cytotoxicity and receptor‑mediated gene delivery into mesenchymal stem cells and transfection efficiencies superior to those presented by native dendrimers and by partially degraded dendrimers.[125]

The protection of DNA from in vivo degradation by the vectors is another key feature for success in gene delivery. Diaz-Mochon et al. [126] showed that a hybrid combination of PAMAM and peptide dendrimers, the so-called peptoid dendrimers, were able to transfect cells with higher efficiency than the PAMAM counterpart, and were nontoxic. In part, this work supported previous findings which demonstrated that combination of primary and secondary amines generates a “proton sponge” effect, which can facilitate theDNAtransfection process, by promoting the release of the plasmid from the cytoplasmic lysosome. Thus, efficiency of dendrimer/DNA complexes may be favored by prolonging the release of plasmid.

As aforementioned, cationic PAMAM dendrimers have proved to efficiently mediate transfection of DNA into a variety of mammalian cells, in vitro. However, as highlighted, the major drawback of high-generation cationic dendrimers is their associated cytotoxicity. Anionic dendrimers, on the other hand, have shown no cytotoxic effect on cells over a broad range of concentrations. Hussain et al.[127] have reported the successful use of ONs conjugated with pentaerythritol-based anionic dendrimers in inhibiting cancer-cell growth. In vitro studies using cancer cells showed that ONs-dendrimer conjugates enhance the cellular uptake, up to four times as compared to that for naked ONs. These data clearly demonstrated that anionic ONs-dendrimer

conjugates may represent attractive alternatives to cationic non-viral vectors for the delivery of gene silencing ONs. However, it is not known whether the system may facilitate the delivery of duplex siRNA for gene silencing by RNA interference.

Vincent et al.[128] investigated the efficacy in cancer therapy of non-viral gene transfer using the anti-angiogenic angiostatin (Kringle 1–3) and tissue inhibitors of metalloproteinases (TIMP) genes. This study revealed that it was possible to inhibit tumor growth and angiogenesis by using PAMAM dendrimers-like superfectant associated with 36-mer anionic oligomers (ON36) for delivering angiostatin and (TIMP)-2 genes.

Luo et al.[129] revealed the low cytotoxicity of PEG-modified PAMAM and their efficiency on the DNA delivery. These systems were obtained using low generation dendrimers with PEG chains, which mimics the fractured high-generation dendrimers. In fact, the proposed molecules showed a 20-fold increase in transfection efficiency as compared to that of partially degraded dendrimer controls.

5. Dendrimers in Cancer Treatment

Dendrimers are attractive vehicles for delivery of antineoplastic agents at their target site. The flexible branches of a dendrimer, when constructed appropriately, can provide a tailored sanctuary containing voids that provide a refuge from the outside environment wherein drug molecules can be physically trapped [130]. Encapsulation of hydrophilic, hydrophobic, or even amphiphilic compounds as guest molecules within a dendrimer [131] can be enhanced by providing various degrees of multiple hydrogen bonding sites or ionic interactions [130] or highly hydrophobic interior void spaces [132].

Covalent linkage of small molecule drug candidates to a dendrimer enhances the pharmacological properties of the drug. In cancer chemotherapy, these desirable size-based features are reinforced by the enhanced permeability and retention (EPR) effect that improves the delivery of macromolecules to tumors.

Folate has been studied as dendrimer-based drug targeting to the cancer cells. Folate is an attractive small molecule for use as a tumor targeting ligand because the membrane-bound folate receptor (FR) is over expressed on a wide range of human cancers, including those originating in ovary, lung, breast, endometrium, kidney and brain [133]. As a small molecule, it is presumed to be non-immunogenic, it has good solubility, binds to its receptor with high affinity when conjugated to a wide array of conjugates, including protein toxins, radioactive imaging agents, MRI contrast agents, liposomes, gene transfer vectors, antisense oligonucleotides, Ribozymes and antibodies [133, 134] . Upon binding to the folate receptor, folate-conjugated drug conjugates are shuttled into the cell via an endocytic mechanism, resulting in major enhancements in cancer cell specificity and selectivity over their non-targeted formulation counterparts [133, 134]. Monoclonal antibodies are also used in dendrimer-based targeting because they recognize and selectively bind to tumor associated antigens (TAAs) [135].

Transferrin is a β-globulin (β1-glycoprotein) and facilitates the transport of ferric ion (Fe3+) through transferring receptors on the plasma membrane. In fact, the use of transferrin as a ligand has been explored as a suitable delivery system for site-specific delivery to tumors[136]. PLL covalently linked with transferrin for delivery of ONs when exposed to human leukemic (HL-60) cells have been stated to promote apoptosis to a greater extent as compared to free ONs.

Another good example of PAMAM dendrimer-based multi-functional devices (target the desire cells, releasing the desired drug and monitoring their internalization fluorescent probe) has been reported by Islam et al. [137]. This group partially acetylated PAMAM dendrimers (G5) that were then conjugated with FITC, FA and MTX. These were devised to target tumor cells through the folate receptor, while releasing an anti-tumor drug intracellularly. They showed that HPLC analysis is a valuable technique to determine the purity and stability of dendrimer-based complexes

Yang et al. [138] synthesized FITC- and biotin-linked PAMAM dendrimer (G5) conjugates and investigated their ability for targeting cancer cells. The bifunctional conjugate (FITC–biotin–dendrimer) exhibited much higher internalization by HeLa cells than the conjugate without biotin. The uptake was found to be energy- and dose-dependent, and could be effectively blocked by dendrimer-conjugated biotin. The results indicate that the biocompatible biotindendrimer conjugate can be a promising nano-platform for therapy and diagnosis of tumors.

An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for covalent attachment of drug molecules to the dendrimer periphery. The drug loading can be tuned by varying the generation number of the dendrimer, and release of the drug can be controlled by incorporating degradable linkages between the drug and dendrimer. For example, encapsulation of the well-known anticancer drug cisplatin within PAMAM dendrimers gave conjugates that exhibited slower release, higher accumulation in solid tumors, and lower toxicity compared to free cisplatin[139]. In this regard, Malik et al. [140] prepared anticancer prodrugs, complexed carboxylate-terminated PAMAM dendrimers with cisplatin. They observed that cisplatin molecules can be released from the dendrimer scaffold by hydrolysis. Moreover, the prodrugs showed sustained release behavior (<1% after 80 h), much greater maximum tolerated dose, bioavailability of cisplatin, and prolonged survival period of tumor-bearing mice. Similarly, Malik and Duncan [141] showed that the dendritic polymer palatinates may be administered intravenously, orally, parentally, subcutaneously, or topically to an animal with a malignant tumor in an amount which effectively inhibits the growth of the tumor. Also, dendritic polymer platinates exhibit high drug efficiency, high drug carrying capacity, good water solubility, good stability on storage, reduced toxicity, and improved antitumor activity *in vivo*. On the other hand, the work of Balogh et al. [142] showed the encapsulation of silver salts within PAMAM dendrimers produced conjugates that exhibited slow silver release rates and antimicrobial activity against *Staphylococcus aureus, Pseudomonas aeruginosa*, and *Escherichia coli* bacteria.

Tuo Wei et al disclosed an original supramolecular nanomicellar system based on the amphiphilic dendrimer AmDM, which is able to effectively deliver the clinical anticancer drug DOX, enhance anticancer activity, and combat drug resistance while obviating systemic toxicity. This AmDM/DOX nanomicelle features several favorable advantages as therapeutic options in cancer therapy, including (*i*) high drug loading. This property is primarily

ascribable to the unique dendritic structure which, upon self-assembly, results in micelles with large, low-density hydrophobic core able to accommodate substantial amount of drugs; (*ii*) small micellar size (10 nm) with narrow size distribution; such small-sized nanoparticles favor deeper penetration into inner tumor regions and concurrently prolong overall circulation time for beneficial accumulation in tumor tissue via EPR effect; (*iii*) rapid and effective cellular uptake mainly via boosted macropinocytosis; (*iv*) enhanced drug release at acidic pH, leading to advantageously promoted drug release at tumor lesions, normally more acidic than healthy tissues; and (*v*) effective inhibition of drug efflux. Based on these multiple advantages, AmDM/DOX micelles can effectively enhance DOX therapeutic efficacy and combat drug resistance. Concomitantly, AmDM/DOX nanomicelles can drastically reduce the systemic toxicity of doxorubicin in vivo through preferential delivery at tumor site via combined EPR effect and acid-promoted drug release. Given these encouraging results, this drug delivery system based on amphiphilic dendrimer AmDM constitutes a concrete promise as a therapeutic entity in cancer treatment[143].

Cancer Targeting imaging and therapy

Choi and coworkers [144] have come up with an innovative mix-and-match scheme that promises to offset this gloomy prediction. These researchers have recently reported a cancer-targeting strategy that is reminiscent of the antibody toxin/immunoconjugate strategy where distinct, but linked, entities are used to first recognize and bind and then subsequently modify a cancer cell. Their strategy, however, has great potential to improve on both the ‘‘targeting’’ and ‘‘payload’’ aspects of cancer therapy by, at first seemingly paradoxically, completely dividing these functions into separate dendritic clusters (Figure 4). The key to this approach was to include a DNA ‘‘zipper’’ on each dendrimer that allows the targeting cluster, composed of folate-derivatized PAMAM in proof-of-concept experiments [145], to be readily combined with the imaging or drug-carrying dendrimer by way of the complementary DNA strand [144]. It can be envisioned that the production of libraries of dendrimers targeted to different cancer-specific biomarkers can be produced by a ‘‘mix-and matched’’ strategy by combining ‘‘off-the-shelf ’’ targeting and drug clusters as needed [146]. Development of easily-customizable nanomedicine platforms that exploit the facile duplex DNA formation for the generation of hybrid nano clusters, thus circumventing the tedious synthesis of multiply-functionalized dendrimers, offers hope that the next ten years will witness rapid expansion of dendrimer technologies that build on the painstaking advances of the past decade.

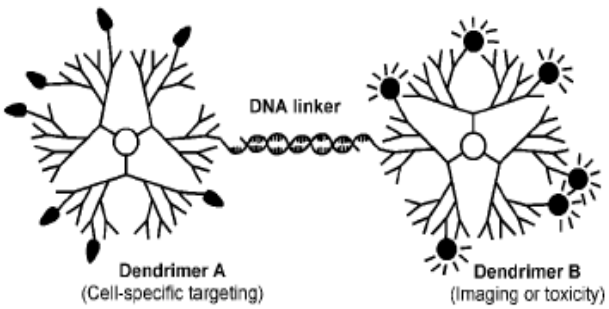

Figure 4: DNA–dendrimer conjugates as potential cancer targeting imaging agents or therapeutics. (Adapted from Ref.[147]) Differentially functionalized dendrimers covalently conjugated to complementary deoxyoligonucleotides can readily form duplex combinatorial nanoclusters that possess cancer cell-specific ligands hybridized to an imaging agent or drug. Cell-specific targeting ligands (e.g., folic acid in one study) are appended to Dendrimer A, and Dendrimer B is conjugated with an imaging agent or drug.

6. Dendrimers in Vaccines Delivery

Most low molecular weight substances are not immunogenic; consequently, when it is desired to raise antibodies against small molecules, they must be conjugated to a macromolecule. In the past, natural proteins have commonly been used as carriers to generate antibodies to small molecules; now an alternative strategy using dendrimers has been demonstrated. In particular, unmodified PAMAM dendrimers that fail to elicit an antibody response on their own become haptenized upon protein conjugation and generate a dendrimer-dependent antigenic response [148,149].

Dendrimers have optimal characteristics to fill the need for efficient immunostimulating compounds (adjuvants) that can increase the efficiency of vaccines. Also dendrimers can provide molecularly defined multivalent scaffolds to produce highly defined conjugates with small molecule immunostimulators and/or antigens [150]. These molecules are ideal carriers of small antigens, making it possible to prepare multimeric antigenic conjugates with well-defined molecular properties for human uses and they do not induce adverse host responses, including immune and/or inflammatory reactions upon administration. The interest has focused on one specific class of dendrimers, namely, the peptide dendrons described in 2005 by Crespo et al. [151].

The basic structure described by Tam [152] is a dendron constructed solely from lysine, taking advantage of the two amino groups (R and *ε*) that are present in each lysine molecule and act as branching points for logarithmic growth. A two-layer dendron thus has four free amino groups and a three-layer dendron has eight, equally divided between Rand *ε*-amino groups. Tam coined the name “major antigenic peptide” (MAP) for such a structure derived from molecules of interest, not only limited to peptides, but also any small molecule that could bind covalently to the terminal amino groups of the MAP “core” dendron.

7. Dendrimers as Ophthalmic vehicles

The majorities of topically applied ocular drug-delivery systems are formulated either as solutions, ointments, or suspensions and suffer from various disadvantages such as quick elimination from the precorneal region, poor bioavailability, or failure to deliver the drug in a sustained fashion. Several research advances have been made in ocular drug delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome some of these disadvantages. Ideal ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, and biodegradable. The viscosity of the final product should be optimized so that the dosage form does not run out of the eye. Dendrimers provide solutions to some complex delivery problems for ocular drug delivery.

Some recent research efforts in dendrimers for ocular drug delivery include PAMAM dendrimers that were studied by Vandamme and Brobeck as ophthalmic vehicles for

controlled delivery of pilocarpine and tropicamide to the eye [153].

PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in improving residence time and enhancing bioavailability of pilocarpine in the eye. [154] In the New Zealand albino rabbit model, the residence time of pilocarpine in the eye was increased by using dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability.

In another study, dendrimer end groups were conjugated with aminosaccharides and sulfated aminosaccharides to obtain anionic dendrimers with unique biological properties [155]. These glucosamine and glucosamine 6-sulfate dendrimers were studied in a rabbit model of scar tissue formation after glaucoma filtration surgery. These unique polymeric macromolecules increased the long-term success of the surgery from 30% to 80% when used together.

In another study, lipophilic amino-acid dendrimers were used to study the long-term effect of use of dendrimer for delivery of an antivascular endothelial growth factor (VEGF) oligonucleotide (ODN-1) to the eye of rats with the aim of inhibiting laser-induced choroidal neovascularization (CNV). It was shown that dendrimer containing ODN-1 showed significantly greater inhibition of CNV over a 4–6 month period compared with ODN-1 alone [156]. Immunohistochemistry of the eye tissue after long-term treatment with dendrimers was conducted to determine if an immune response was generated after use of the dendrimer as a drug conjugate for treating eye diseases. It was determined that there was no significant increase in inflammatory response, proving that dendrimers could be used as a viable option for delivery of oligonucleotide to the eye for treating angiogenic eye diseases without concern of generating unwanted biological response.

8. Dendrimers in Topical and Transdermal delivery

Dendrimers have found recent applications in novel topical and transdermal delivery systems, providing benefits such as improved drug solubilization, controlled release, and drug-polymer conjugates (pro-drugs). The viscosity-generation-number property of a dendrimer solution allows for ease of handling of highly concentrated dendrimer formulations for these applications. Dendrimers have been shown to be useful as transdermal and topical drug delivery systems for nonsteroidal anti-inflammatory drugs (NSAIDs), antiviral, antimicrobial, anticancer, or antihypertensive drugs. PAMAM dendrimers have been studied as carrier transdermal systems for the model NSAIDs: ketoprofen and diflunisal [157]. It was found that the PAMAM dendrimer-drug formulations showed increased transdermal drug delivery compared with formulations lacking dendrimers. *In vivo* studies in mice showed prolonged pharmacodynamic responses and 2.73-fold higher bioavailability over 24 h for certain dendrimer-containing drug solutions.

In another study, transport of indomethacin through intact skin was enhanced *in vitro* and *in vivo* [158]. The bioavailability of indomethacin was increased by using G4-PAMAM dendrimers with terminal amino groups. There have also been studies where dendrimers failed to show enhancement in drug transport through intact skin. It is well known that the molecular diffusion through intact skin is related to the molecular weight of the permeant molecule. Because of their high molecular weights, dendrimers generally have low diffusion coefficients. Diffusion through skin is more favorable for molecules that have solubility in lipids as well as in water. It could be possible to synthesize dendrimers with appropriate physical-chemical properties to facilitate drug transport through intact skin. Dendrimers with such favorable physicochemical properties could enhance transdermal transport of drugs by this mechanism. More research is warranted in this area to understand the structural-activity relationship of dendrimers in relation to skin transport.

In contrast to transdermal delivery, the use of dendrimers for topical delivery to the skin has shown to be more promising. Two different kinds of dendrimers were shown to have antiviral activity *in vitro* when the dendrimers were added to the cells before being challenged with the viruses. The dendrimers studied were either PAMAM or polylysine dendrimers. In contrast, dendrimers added to the cells after they were challenged with the virus showed no antiviral activity. The study was carried out in an *in vitro* assay to determine dendrimer activity against herpes simplex virus (HSV) types 1 and 2. When tested in human foreskin fibroblast cells, both PAMAM and polylysine dendrimers showed activity against the virus. This study suggested that dendrimers could potentially be used as topical microbicides to be applied to the vaginal or rectal mucosa to protect against sexually transmitted diseases such as HIV or genital herpes. When tested against genital HSV infection in mice, two of the compounds showed significant reduction in infection rates when applied prior to intravaginal challenge.

Dendrimers are able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently due to its highly water soluble and biocompatible nature. For example improving the drug permeation 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[157,158].

9. Dendrimers in Pulmonary drug delivery

Polyamidoamine dendrimers with positive charge have shown the enhanced bioavailability in pulmonary delivery of low-molecular weight heparin (a negatively charged oligosaccharide) to treat vascular thromboembolism. In this formulation, dendrimer-drug complex was formed [159]. Further studies showed that heparin encapsulated in pegylated dendrimers has a longer circulating half-time and increased pulmonary absorption [160].

Pegylated dendrimeric micelles prolong the half-life of low molecular weight heparin (LMWH), Enoxaparin and increase the drug's pulmonary absorption, thereby efficacious in preventing deep vein thrombosis (DVT) in a rodent model. Shuhua Bai have prepared dendrimers of LMWH entrapped in PEG these produced a significant increase in pulmonary absorption and the relative bioavailability of the formulation was 60.6% compared to subcutaneous LMWH. The half-life of the PEG–dendrimer-based formulation was 11.9 h, which is 2.4-fold greater than the half-life of LMWH in a saline control formulation. When the formulation was administered at 48-h intervals, the efficacy of LMWH encapsulated in pegylated dendrimers in reducing thrombus weight in a rodent model was very similar to that of subcutaneous LMWH administered at 24-h intervals [161]

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In addition to dendrimers, cationic liposomes were used as carriers for heparin and showed enhanced pulmonary absorption. These cationic liposomes were prepared by conventional methods, i.e. lipid dispersion, solvent evaporation and extrusion [162].

10. Dendrimer as Solubility enhancer

With the discovery of new drug molecules today low solubility is the main hurdle to be overcome[163]. Approximately 40% of newly developed drugs are rejected by the pharmaceutical industry and will never benefit a patient because of low water solubility. Given the growing impact and need for drug delivery, a thorough understanding of delivery technologies that enhance the bioavailability of drugs is important. The high level of control over the dendritic architecture (size, branching density, surface functionality) makes dendrimers ideal excipients for enhanced solubility of poorly water-soluble drugs. Many commercial small-molecule drugs with anticancer, anti-inflammatory and antimicrobial activity have been formulated successfully with dendrimers, such as poly (amidoamine) (PAMAM), poly(propylene imine) (PPI or DAB) and poly(etherhydroxylamine) (PEHAM). Some dendrimers themselves show pharmaceutical activity in these three areas, providing the opportunity for combination therapy in which the dendrimers serve as the drug carrier and simultaneously as an active part of the therapy. Dendrimers are unimolecular micellar nature, due to have hydrophilic exteriors and hydro-philic interiors and form covalent as well as non-covalent complexes with drug molecules and hydrophobes, and enhance its solubilisation behaviour[164].

11. Dendrimers in Cellular delivery

PAMAM dendrimers with lauryl chains to reduce toxicity and enhance cellular uptake, for example Dendrimer ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus>3 hr), suggesting that dendrimers can efficiently carry the complexes drug inside cells[165].

12. 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 bio assemblies 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. Generation 2 dendrimer matches the width (2.4 nm) of DNA duplexes (form stable complexes with histone clusters to condense and store DNAwithin the nucleosome of cells.) and generations 5 and 6 PAMAM dendrimers have diameters approximately equivalent to the thickness of lipid bilayer membranes (~5.5 nm) of biological cells[166, 167].

13. 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 transmitted diseases (STDs) when Poly(lysine) dendrimers modified with sulfonated naphthyl groups. Show potent antibacterial biocides against Gram positive and Gram negative bacteria when PPI dendrimers with tertiary alkyl ammonium groups attached to the surface and Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications[168].

14. Dendrimers in Site Specific Drug Delivery

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems[169]. The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug[170].

The targeted delivery of chemotherapeutics is essential to reduce the side effects significantly associated with conventional therapy, where healthy tissues such as liver, spleen, kidneys and bone marrow can accumulate the toxic levels of drug. The site specific delivery of the drug could be achieved by surface modification of dendrimers employing various targeting moieties such as folic acid (FA), peptides, monoclonal antibodies and sugar groups.[171] Several successful active and passive targeting attempts were accomplished by engineering the branching units and surface groups of dendrimers. Patri et al. conjugated FA to G5 PAMAM dendrimer for the targeted delivery of methotrexate and observed receptor mediated drug delivery that demonstrated high specificity for KB cells overexpressing folate receptors and showed slower drug release.[35] The authors further conjugated the PhiPhiLux G1 D2, an apoptotic sensor to FA attached PAMAM dendrimers which showed 5 fold enhanced fluorescence, attributed to successful delivery of drug with cell‑killing efficacy.[172]

pH and temperature-activated polymers are known to be successful drug delivery systems. Photochemical internalization (PCI) can facilitate site-specific delivery, e.g., escape of the macromolecules from endocytic vesicles into the cytosol. Lai et al. [173] conjugated doxorubicin (Dox) to PAMAM dendrimers via pH-sensitive and insensitive linkers, acid-labile hydrazone linkages (PAMAMhyd- Dox) and amide (PAMAM-amide-Dox), respectively.

They combined doxorubicin-dendrimers with different PCI strategies to evaluate the cytotoxic effects. Results showed that both PCI strategies promoted the PAMAM-amide-Dox cytosolic distribution, but significantly enhanced the cytotoxicity of free Dox on human gingival cancer (Ca9-22) cells at higher concentrations. The authors failed to develop a multi-modality cancer treatment, but their data provided insights on possible research directions, namely the need to exploit spacers other than amide-linkage in drug-polymer complexes.

Wiwattanapatapee et al. [174] investigated the use of dendrimers for colon-specific drug delivery applications. In their studies, 5-aminosalicylic acid (5-ASA) was bound to the water-soluble dendrimer using different spacers containing azo-bond (e.g., p-aminobenzoic acid, PABA and p-aminohippuric acid, PAH). PAH provide the polymer conjugates a higher loading capacity (3 times) for 5-ASA as compared to that of dendrimer conjugates with PABA as the spacer. In vitro studies of rats with cecal content were carried out to investigate drug release from dendrimer conjugates. The release of 5-ASA from both conjugates was significantly slower as compared to that of sulfasalazine (SA), a commercial prodrug. Moreover, the

conjugate with PAH linker showed significantly higher amount of initial drug release than the conjugate with the PABA linker. As a consequence, the amount of drug released from PAMAM-PAH-SA was significantly higher than that of PAMAM-PABA-SA conjugate. This study nicely illustrated the potential use of PAMAM dendrimer for colon-specific drug delivery, and the important role of the spacers for the optimization of drug release.

CD derivatives bearing peptides may be useful as carriers for transporting drugs to biological targets containing specific peptide receptors. Thus, peptide biorecognizability together with the CD host–guest complexation properties makes such systems suitable templates for the application in site-specific drug delivery. Much effort has beenmadeto complex low generation dendrimers with other polymers. For example, Dodziuk et al. [175] reported attempts to complex a first-generation dendrimer having four branches with α, β or γ cyclodextrins, found to be unsuccessful in their subsequentNMRstudies. Muhanna et al. [176] reported a different strategy, with the synthesis of tetradecavalent amino acid and peptide dendrimers based on a β -CD core. These were found to have great potential for application in MAP concept as a means to increase the peptide–receptor binding, and hence improve the site specificity of the drug delivery system.

DENDRIMERS IN DIAGNOSIS:

1. Dendrimers as molecular probes

Due to their distinct morphology and unique characteristics, use as molecular probes. 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[177].

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[178, 179].

3. Dendrimers as MRI contrast agents

Magnetic resonance imaging (MRI) is an important tool in modern medicine, providing high-quality three-dimensional images without the use of harmful ionizing radiation. The signal intensity in MRI stems mainly from the relaxation rate of *in vivo* water protons and is enhanced by the administration of a contrast agent prior to the scan. Such agents include a paramagnetic metal ion that decreases the relaxation times of nearby water protons. Different groups of contrast agents are established for clinical application: gadolinium chelates, superparamagnetic iron oxide particles, and hepatobiliary contrast agents. However, the gadolinium chelates constitute the largest group of MRI contrast agents and are considered to be safe.

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[180,181].

The crucial properties of MRI contrast agents include good biocompatibility, low toxicity, and high relaxivity. Low molecular weightMRI contrast agents diffuse rapidly from blood vessels into the interstitial space and are excreted fromthe body very rapidly [94]. Paramagnetic metal chelates such as Gd(III)-N,N□,N□□,N□□□-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane (Gd(III)-DOTA), Gd(III)-diethylenetriamine pentaacetic acid (Gd(III)-DTPA), and their derivatives are used as contrast agents for magnetic resonance imaging (MRI), because these metal chelates increase the relaxation rate of surrounding water protons [182].

However, the shortcomings of these low molecular weight contrast agents include short circulation times within the body and inefficient discrimination between diseased and normal tissues. Subsequently, macromolecular Gd(III) complexes have been developed by conjugating Gd(III) chelates to biomedical polymers, including poly(amino acids), polysaccharides, and proteins to improve image contrast enhancement. These macromolecular agents have demonstrated superior contrast enhancement for blood pool imaging and cancer imaging in animal models. Unfortunately, the clinical application of macromolecular agents in general is limited by their slow excretion rate which results in their accumulation within the body, that is, the liver. In addition, the long residence time of MRI agents enhances the risk of potential toxicity by Gd(III) ions released during the metabolism of these agents [183], [184].

On the other hand, Wiener et al. [185] developed a new class ofmagnetic resonance imaging contrast agents,Gd(III)-DTPA-based PAMAM dendrimers, with large proton relaxation enhancements and high molecular relaxivities. These 6th generation PAMAM dendrimers possess 192 reactive terminal amines,which can be conjugated to the chelating ligand 2-(4-isothiocyanato-benzyl)-6-methyl-(DTPA) through a thiourea linkage. This dendrimer has a relaxivity a six times higher than that of free Gd(III)-DTPA complex. *In vivo* experiments on rabbits show excellent MRI images of blood vessels and long blood circulation times (>100min) upon intravenous injection. In addition,Kobayashi et al. [186] synthesized small dendrimer-based MRI contrast agents and investigated the relationship between relaxivity and dendrimer generations using Gd(III)-DTPA based PAMAM dendrimers. The results of this study revealed that relaxivities increased as the dendrimer generation increased, but there was no significant increase in relaxivities beyond 7th generation.

4. Dendrimers for CNS Imaging and Diagnosis

Imaging of CNS is an important tool for studying and monitoring the structure and functional changes in the brain and spinal cord. Advanced imaging can lead to a better understanding of the effect of cellular damage on CNS function and can help to improve the precision of neurological procedures.[187,188] To date, surgical resection remains the main treatment for brain tumors. The success of brain tumor removal during surgery is highly dependent on the surgeon's ability to differentiate tumor from normal tissues using subjective criteria that are not easily quantifiable. A recent interesting report revealed that Cy5-labeled free activatable cell-penetrating peptides (ACPPs) conjugated to PAMAM dendrimers delineated the margin between tumor and adjacent tissue and thereby improved the precision of tumor resection in mouse xenograft models.[189,190]

Contrast enhanced magnetic resonance imaging (MRI) is widely used for defining brain tumors in the clinic, but its ability to be used in tumor visualization is limited by the transient circulation life time, nonspecificity, and poor BBB permeability of the commercially available MRI contrast agents. Because the brain is the most complex organ in human body, the precision of brain tumor resection becomes more crucial and relevant than ever. It is of interest and the utmost urgency to investigate further dendrimer application in brain tumor imaging. In addition, the complete excision of a malignant brain tumor is also challenged by its infiltrative nature. Interest in nanoparticles has grown for the development of new imaging and diagnostic agents for the assessment of brain function and diagnosis of CNS disorders and diseases using structural imaging techniques, such as MRI, computed tomography (CT), positron emission tomography (PET), magnetoencephalography (MEG), and optical imaging.[188] Nanoparticles have been developed that have better body-compartment distribution and tissue targeting than standard contrast agents.[191]

Theoretically, nanoparticles used in drug delivery can be applied to deliver imaging agents and diagnostic molecules. Consequently, increasing attention has been paid to the development of nanoparticles that can fulfill multiple functions including therapy, imaging, and diagnosis. In addition to the extensive studies of dendrimers in drug delivery, the development of dendrimer-mediated CNS imaging and diagnosis has attracted considerable attention.[192,193]

PAMAM-PEG-T7 was explored to deliver MRI contrast agents to liver and early brain glioma tumors.[194] PAMAM-PEG-T7 was conjugated with diethylene triamine pentaacetic acid (DTPA) and further chelated gadolinium (Gd) to yield Gd-DTPA-PAMAM-PEG-T7. The MRI results showed that Gd- DTPA-PAMAM-PEG-T7 could selectively identify liver cancer but not early glioma, suggesting that this nanoscaled MRI contrast agent might allow for selective and efficient diagnosis of tumors without the natural barrier.[194] To overcome this natural barrier, a two-component targeted nanoprobe was developed on the basis of PAMAM dendrimer (G5) labeled with MR/optical imaging reporters and tumor vasculaturetargeted cyclic (RGDyK) peptides and angiopep-2 peptides.[195]

It has been reported that brain tumor cells highly express both αVβ3 integrin and LRP receptor.[196,197] This nanoprobe first targets the αVβ3 integrin expressed in the tumor vasculature. Second, the increased local concentration of the nanoprobe facilitates the association between angiopep-2 peptides and LRP receptors on the vascular endothelial cells and further accelerates the BBB transversing of the nanoprobe via LRP receptor-mediated endocytosis. In vivo imaging studies illustrated that this nanoprobe could efficiently cross the intact

BBB in normal mice and precisely delineate the boundary of the orthotopic U87MG human glioblastoma xenograft with a high target-to-background signal ratio.[195] Another macromolecular MRI contrast agent was developed on the basis of dendrigraft poly-L-lysines (DGLs) modified with chlorotoxin (CTX) and a tumor-specific ligand and loaded with Gd-DTPA as a contrast agent. The MRI results showed that both signal intensity and duration were significantly enhanced in tumorbearing nude mice treated with CTX-modified contrast agent compared to those treated with an unmodified counterpart and a commercial control. Ion imaging is another powerful methodology to assess fundamental biological processes in live cells. However, this approach is limited by the efficiency of some ion-sensing probes and the fast leakage from cells. A dendrimer-based nanoparticle was developed to achieve better intracellular retention of fluorescent probes and to perform prolonged fluorescence imaging of intracellular ion dynamics.[198]

A sodium dye, CoreNa Green, was encapsulated within a PEGylated PAMAM dendrimer (G5) to generate a sodium-sensitive nanoprobe. This nanoprobe is very stable and possesses high sodium sensitivity and selectivity. This nanoprobe homogenously filled the entire cell volume and remained for a long duration without detectable alterations of functional cellular properties when it was loaded in neurons in live brain tissue. The same principle can be applied to other existing fluorescent dyes, generating new applications for live fluorescent imaging. [198]

In addition to their straight forward assembly, dendrimer based nanoprobes are promising for the noninvasive visualization of brain tumors with uncompromised BBB, providing the possibility for real-time optical-image-guided brain tumor resection during surgery. Thus, dendrimer-based nanoprobes could become an attractive tool for CNS imaging and diagnosis.

THERAPEUTIC APPLICATION OF DENDRIMERS

1. Dendrimers in photodynamic therapy (PDT)

In PDT Cancer treatment involves the administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue. PDT has been shown to reduce tumors by direct cell killing, destruction of tumor neovasculature, and triggering of an acute inflammatory response that attracts leukocytes to the tumor [199]. For example the photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes.

Dendrimers have been used as carriers for improved delivery of 5- aminolevulinic acid (a natural precursor of photosensitizer protoporphyrin 1X) that increases the accumulation of porphyrin in cells, which further results in toxicity.[200-200] Recently, polymeric micelles encapsulating dendrimer phthalocyanine have been developed as a photosensitizer formulation for enhanced photodynamic effect.[203]

More recently, G3 PAMAM grafted porous hollow silica nanoparticles (PHSNPs) were successfully fabricated as photosensitive drug carriers for PDT. The attachment of gluconic acid (GA) to this system was thereafter followed, for surface charge tuning. PAMAM- functionalized outer layer with a large number of amino groups provided high loading amount of aluminum phthalocyanine tetrasulfonate (AlPcS4), its retarded premature release and effective release to target tissue. The study demonstrated that irradiation of the AlPcS4 entrapped GA- G3- PHSNPs with light resulted in efficient generation of singlet oxygen that produced significant damage to tumor cells and suggested as effective photosensitizer formulation for PDT applications.[204]

2. Dendrimers for boron neutron capture therapy (BNCT)

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Boron therapy is concerned with the treatment of cancers that is based on Boron capture reaction[205]. 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. Due to their well defined structure and multivalency, Dendrimers are a very fascinating compound for use as boron carriers[206].

The applicability of PAMAM dendrimers in investigating intratumoral delivery of agents for neutron capture therapy is remarkable in biomedical science. In a study by Wu et al. functionalized G5 PAMAM dendrimers and conjugated cetuximab specific to EGF receptor to starburst dendrimers that carried around 1100 boron atoms. The in vivo results revealed that accumulation of conjugates were 10 times higher in brain tumor tissues in comparison to healthy brain tissues. This study was first to demonstrate the efficacy of a boronated monoclonal antibody for boron neutron capture therapy of an intracerebral glioma.[207] Dendrimer based boron neutron capture therapy in combination with EGF receptor targeting moieties can enhance the boron uptake in tumor tissues.[208]

A similar strategy (e.g., cell targeted particles) was followed by Wu et al. [209], developed a vehicle for boron neutron capture therapy (BNTC). A heavily boronated PAMAM dendrimer was chemically linked to C225 by means of the heterobifunctional reagents N-succinimidyl 3-(2-pyridyldithio)-propionate and N-(k-maleimido undecanoic acid)-hydrazide. Initial in vitro studies revealed that the F98EGFR glioma cells mentioned above specifically internalize the particles when compared to receptornegative F98 wild-type cells. Further in vivo studies were conducted by stereotactically implanting F98EGFR cells into the brains of Fischer rats. The targeted boronated dendrimers were administered 14 days after either convection enhanced delivery (CED) or direct intratumoral (i.t.) injection. Results revealed that not only were the targeted dendrimers receptor specific in vivo, but also that animals exposed to the tested therapy displayed higher survival rated when compared to controls. In this sense it appears that this strategy for using dendrimers as targeted particles for therapeutic usage is more favorable than the former.

3. Gadolinium-based (Gd) neutron capture therapy (GdNCT)

It is an alternative to BNCT that has been investigated due to Gd's high neutron absorbency properties, but has rarely been used as it is deemed too difficult to achieve therapeutic doses intravenously. Kobayashi et al. explored Gd-labeled PAMAM dendrimers for the delivery of MRI contrast agents that may also facilitate the use of neutron capture therapy to the sentinel lymph node, which is often imaged for breast cancer management[210,211]. Generation 2, 4, 6, and 8 PAMAM dendrimers, ranging in sizes from 3 to 12 nm, were evaluated to determine the optimal particle size for entering the lymphatic vessels while avoiding leaking, and it was shown that G6-PAMAM (9 nm) produced the earliest and most intense opacification of the sentinel lymph nodes with sufficient Gd concentrations for NCT. Conversely, G2- and G4 PAMAM do not retain in the lymphatic vessels, while G8-PAMAM is too large for rapid uptake. Based on these results, it was determined that gadolinium-labeled G6-PAMAM may simultaneous image and treat primary tumors or micro-metastasis in the sentinel lymph nodes.

4. Dendrimeric-based artificial virus receptors

Research on dendrimeric-based artificial virus receptors has attracted great deal of attention. Yamada et al. [212] successfully synthesized a novel class of carbosilane dendrimer periphery-functionalized lacto-N-neotetraose, aimed to mimic dengue virus receptor. In another work [213], they synthesized carbosilane dendrimers peripheryfunctionalized with lactotriaose (GlcNAc#1-3Gal#1-4Glc) with valencies of three, four, six, and 12 for use in a lectinbinding assay. The hexavalent glycodendrimer showed a 2500-fold larger binding effect than that of free lactotriaose, though the dodecavalent one exhibited only a 1200-fold larger binding effect. The same group also reported [214] on the potential of carbosilane dendrimers periphery-functionalized with galabiose (three, four, and six galabiose residues) for use as artificial inhibitors against Shiga toxins.

Bhadra et al. [215] synthesized PPI dendrimers-coated with galactose and investigated the efficiency on delivering primaquine phosphate (PP, a liver schizonticide) directly to liver cells. The results showed that the coating of PPI systems with galactose increases the drug entrapment efficiency, prolonged circulation and drug release as compared to uncoated PPI delivery systems.

Agrawal et al. [216] demonstrated a method to synthesize galactose-coated PLL dendrimers having polyethyleneglycol (PEG-1000) as core. This method consisted on alternating protection and deprotection steps of l-lysine by di-tert-butyl dicarbonate (di-BOC) until the formation of peptide dendrimer (G4) took place. Moreover, they successfully loaded these macromolecules with chloroquine phosphate, which is extensively employed for the suppression and treatment of malaria. The internalization studies of uncoated and coated drug dendrimer formulations in macrophages revealed almost 5 times reduced phagocytosis due to galactose coating. Galactosecoated peptide dendrimers drastically reduced haemolytic activity compared to uncoated PLL formulation. Haematological data suggested that galactose-coating strategy decrease immunogenicity as compared to uncoated formulations.

DENDRIMER IN THERANOSTICS: DENDRIMER BASED COMBINED DIAGNOSIS AND THERAPY

Recently, a combination of polymer chemistry and imaging science approaches has led to the generation of polymer-based bioimaging probes for the diagnosis and treatment of different diseases. The ultimate goal of in vivo imaging is to achieve highly sensitive and reliable imaging techniques viable for diagnosis in personalized medicine for delivering drugs, following their distribution, and monitoring therapy. This concept (theranostics) is based on the “find, fight and follow” approach[217]. New probes with enhanced capabilities and performance should be developed specific to nano-imaging techniques. Key research priorities for targeted delivery and in vivo imaging should address: (i) design of nanostructures with stealth properties that prevent them from being opsonised or cleared before reaching the target cells, (ii) ability to penetrate into cells and crossover biological barriers like the BBB, uptake and recycling of nanostructures, (iii) nanocarriers or strategies that selectively targets diseased cells, tissues and organs, (iv) trans-endocytosis of nanostructures, (v) safety evaluation (in vitro/in vivo cytotoxicity, haemocompatibility and immunogenicity), in vivo carrier biodistribution, and (vi) compatibility with external activation by magnetic field,

ultrasound, X-ray, or optics to trigger the therapeutic activity. For example, the Kobayashi et al. [218] have shown that a dendrimer-based magnetic resonance contrast agent may be useful for in vivo detection of renal tubular damage.

Rietveld et al. [219] developed dendrimers with tetrabenzoporphyrin cores for in vivo oxygen imaging. While it is promising to incorporate both therapeutic agents and molecular-tags on the dendrimers, and improve their potency [210], the possibility of combining diagnosis and therapy in multi-functional dendrimer-based nanosystems can allow the early detection, targeting and treatment of several diseases.

Thomas et al. [221] have linked PAMAM dendrimers (G5) with FITC for tracking, and two different antibodies, 60bca and J591, which bind to CD14 and prostrate specific membrane antigen (PSMA), respectively. This work showed the receptor specificity as the conjugates bound to specific antigen expressing cells. Shukla et al. [222] synthesizedPAMAMdendrimers (G5) conjugated to anti-HER2 monoclonal antibody by tagging the formulation with alexaFluor (AF). Flow cytometry studies revealed the uptake of conjugate by HER2 expressing cells, while no such affinity was found for MCA-207 control cells that did not express HER2, in vitro. Another good example of such versatile dendrimeric systemswas put forward by Baek and Roy [223].

A well-defined multivalent T-antigen (Thomsen-Friedenrich antigen)-glycoPAMAM dendrimer was synthesized, aimed at applications in the detection and immunotherapy of carcinomas such as breast cancer. In another study [224], they synthesized a heterobifunctionalized dendritic l-lysine core bearing biotin and T-antigen by coupling the thiolated T-antigen derivative to N-chloroacetylated glycylglycyl llysine dendritic cores. According to the literature, the success of entrapping small molecules inside the dendrimer depends on the mutual properties between the host and the guest molecules. For example, Domanski et al. [225] reported attempts to entrap small fluorescent-probes commonly used to evaluate membrane fluidity inside the dendrimer. This work showed that 12-(9-anthroyloxy) stearic acid (12-AS), a non-polar fatty acid derivative, was successfully incorporated into the PAMAM dendrimers cavities, while on the contrary, 1 (trimethylammoniumphenyl)-6- phenyl-1,3,5 hexatriene p-toluenesulfonate (TMA-DPH), a amphiphilic salt possessing a positive charge, was not.

Transferrin is a β-globulin (β1-glycoprotein) and facilitates the transport of ferric ion (Fe3+) through transferring receptors on the plasma membrane. In fact, the use of transferrin as a ligand has been explored as a suitable delivery system for site-specific delivery to tumors [226]. PLL covalently linked with transferrin for delivery of ONs when exposed to human leukemic (HL-60) cells have been stated to promote apoptosis to a greater extent as compared to free ONs. Another paper [227] demonstrated that PEGylated poly(cyanoacrylate) nanoparticles conjugated to transferrin were effective on the delivery of paclitaxel (PTX), an anti-tumor drug. PEGylation prevented aggregation of nanoparticles and transferrin effectively determined tumor site. An innovative study by Choi et al. [144] consisted of the development of dendrimers conjugated to different biofunctional moieties [FITC for imaging, and folic acid (FA) for targeting], linked together using complementary DNA oligonucleotides to produce clustered molecules for targeting tumor cells through folate receptors. This step forward allowed obtains both efficient DNA-linked dendrimer clusters for intracellular imaging and therapeutics, and circumvent the tedious synthesis of multiply-functionalized dendrimers.

Instead of linking oligonucleotides to the dendrimers, Majoros et al. [228] synthesized amulti-functionalPAMAM dendrimer (G5) conjugated with FITC, FA, and PTX. In vitro studies have shown that drug-free dendrimer conjugates were not cytotoxic even at high concentrations. On contrary, drug-loaded dendrimer conjugatesweretoxic to both folate receptor-positive and folate receptor-negative cells as a result of non-specific binding at concentrations around 200 nM. Another good example of PAMAM dendrimer-based multi-functional devices (target the desire cells, releasing the desired drug and monitoring their internalizationfluorescent probe) has been reported by Islam et al. [229]. This group partially acetylated PAMAM dendrimers (G5) that were then conjugated with FITC, FA and MTX. These were devised to target tumor cells through the folate receptor, while releasing an anti-tumor drug intracellularly. They showed that HPLC analysis is a valuable technique to determine the purity and stability of dendrimer-based complexes.

Yang et al. [138]synthesized FITC- and biotin-linked PAMAM dendrimer (G5) conjugates and investigated their ability for targeting cancer cells. The bifunctional conjugate (FITC–biotin–dendrimer) exhibited much higher internalization by HeLa cells than the conjugate without biotin. The uptake was found to be energy- and dose-dependent, and could be effectively blocked by dendrimer-conjugated biotin. The results indicate that the biocompatible biotindendrimer conjugate can be a promising nano-platform for therapy and diagnosis of tumors.

Epidermal growth factor (EGF) is an important factor that controls the disposition of neoplastic cells and potentiates transcription and proliferation of cells. Human growth receptor (HER-2) is amember of EGF family and their number is augmented in several tumors [230], and hence, it provides a potential target for immunotherapeutic agent.

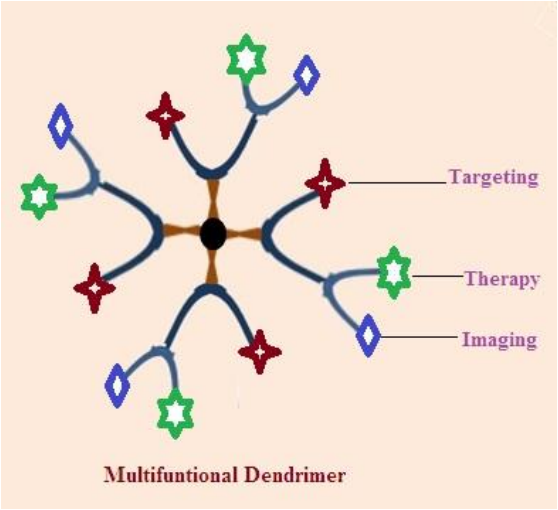

Figure 5: Multifuntional dendrimer

Nanoparticles having a size in the range 1–10nm have the capacity to diffuse into tumor cells. This helps to overcome limitations relating to chemotherapy using free drug such as poor in vivo/in vitro correlation and overcome other possible resistances offered by tumors. In fact, Tomalia [231]

has also proposed the use of ~5nm sodium salt-PAMAM dendrimers (G4.5) nanoparticles possessing a 1,4-diaminobutanecore, as multi-purpose nanodevices for oncology drug delivery and diagnostic MRI contrast agents.

OTHER BIOMEDICAL APPLICATION OF DENDRIMERS

1. *Dendrimers in Tissue Engineering:*

The aim of tissue engineering applications is for the encapsulated cells to regenerate native extracellular matrix (ECM) and eventually replace the scaffold altogether. Therefore, the scaffold must biodegrade at a rate that complements the biosynthesis of new ECM.

Polymeric scaffold compositions can be divided into two main categories: natural and synthetic. Natural scaffolds are constructed from proteins, carbohydrates, or glycoproteins. Collagen is the most commonly used protein for scaffold construction [232]. Fibrin is another protein used for scaffold construction due to its ability to assemble into mesh-like networks. Hyaluronic acid and chondroitin sulfate are key structural components and have been used extensively as tissue engineering scaffolds. Carbohydrates such as alginate [233], dextran [234], and chitosan [235] are also used as scaffold materials due to their ability to form hydrated networks. The synthetic linear polymers, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(caprolactone) (PCL), and poly(ethylene glycol) (PEG) have also been used extensively as scaffold materials [236].

Kim et al. [237] also investigated the response of human epithelial cells to dendrimer-immobilized substrates, with or without D-glucose displayed as a terminal ligand. When the topographic surface possessed a roughness of 4 nm, epithelial cells cultured on naked dendrimer surface without D-glucose were somewhat stretched in their morphology compared with those on a non-modified plain surface. However, for the roughness values higher than 4nm cell stretching was inhibited, thus resulting in the predominance of round-shaped cells. The change in cell morphology was quite evident on the surfaces with D-glucose-displayed dendrimers. Fluorescence microscopic observation showed that when the roughness value increased up to 4.5nmon these surfaces, an enhancement of cell stretching occurs. These results suggested that surface roughness and D-glucose display induce changes in cellular morphology caused by the cytoskeleton formation accompanied by marked cell elongation. Therefore, this study demonstrated that dendrimer surfaces can offer a promising design for optimizing cells culture conditions.

Benhabbour et al. [238], demonstrated that cells showed a greater affinity for the dendronized surfaces as compared to Au surfaces (control). Moreover, in vitro cell culture studies with mouse 3T3 fibroblasts showed that cell attachment was diminished for the PEG-grafted Au surfaces as compared to the control Au and G1–G4 dendronized surfaces. These results showed that dendronized surfaces presenting a large number of hydroxyl groups can be a reliable alternative to the use of peptides to promote cell-adhesion and proliferation.

2. *Dendrimers in Cell Repair:*

Intact extracellular matrices (ECMs) have demonstrated potential as biomaterials in various tissue engineering and clinical applications [239]. These ECM scaffolds provide a natural three-dimensional support to aid the initial mechanical requirements necessary to support damaged or excised tissue [240]. In addition, ECM provides vital biological cues for cellular recognition which is essential for initial cellular attachment, subsequent cellular differentiation, in-growth of vascular networks, and secretion of new ECM requisite for eventual scaffold remodeling and tissue regeneration. Dendrimer works as a linker to the scaffold and as a carrier of bioactive molecules. The dense functional groups terminated on surface of dendrimers can react with intrinsic functional groups in protein-based scaffolds to form covalent binding. Conveniently in this way, scaffold stability can also be tailored by controlling the extent of cross-linking, which has the benefit of extending their *in vivo* life [241].

Availability of multiple functional groups effectively amplifies the number of sites available for conjugation with exogenous bioactive molecules. For example, Chan et al. [242] used generation 1 polyamidoamine (G1 PAMAM)dendrimer as amodel dendrimer and incorporated into cholecyst-derived extracellular matrix (CEM), a novel intact extracellular matrix derived from the perimuscular subserosal connective tissue of porcine cholecysts developed in their laboratory [243]. They observed the incorporation of varied feed concentrations of PAMAM dendrimer in CEM using the EDC/NHS cross-linking system resulted in covalent binding of PAMAM on CEM. Varied degrees of cross-linking, improved stability of CEM to enzymatic degradation, increased amine functional groups useful in tethering bioactive agents, maintenance of tensile strength but increased flexibility of scaffold, and preservation of the ability of DENCEM to support cells *in vitro* were observed.

On the other hand, Boduch-Lee et al. [244] showed the design and synthesis of star polycaprolactone-hydroxyapatite films for use as a biodegradable matrix for bone tissue engineering. They used a hybrid scaffold composed of poly(caprolactone) (PCL) chains conjugated to a poly(Llysine) dendritic core to fabricate an HA-composite for *in vitro* bone regeneration. The effect of these scaffolds was evaluated in the cell line MG-63. They observed that the dendrimer-PCL HA hybrid performed much better than linear PCL, suggesting that the dendritic architecture presents advantages over linear polymers for the purposes of *in vitro* bone cell growth and adhesion over 24 hours.

3. *Dendrimers in Blood Substitution*

Dendrimers are also being investigated for use as blood substitutes. Their steric bulk surrounding a heme-mimetic centre significantly slows degradation compared to free heme[245,246] and prevents the cytotoxicity exhibited by free heme.

4. *Cosmetics and personal care applications*

Because of their excellent carrier properties, dendrimers have utility in cosmetics and personal care products such as hair-styling gels, shampoos, sunscreens, and anti-acne products. Cosmetic compositions comprising hydroxyl-functionalized dendritic macromolecules are described in a patent filed by Unilever's Home & Personal Care division for application in a hair-styling spray, gel, or mousse formulation [247]. The dendritic macromolecules indicated for the hairstyling application in this patent use the polyhydric polyester alcohol or hyperbranched polyol functionalized groups. Another patent filed by L'Oreal described terminal

hydroxyl functional group polyester dendritic macromolecules in combination with film-forming polymers for use in cosmetic and dermatological products intended for application to the skin, keratinous fibers, nails, or mucous membranes [248]. Such a combination of a film-forming polymer with a dendritic polymer allowed the inventors to develop a low-viscosity product that was easily applied to the intended topical skin site and that formed a dry film capable of being peeled-off after the application period. This property allowed for superior cosmetic product performance and ease of use. Here, the unique ability of dendrimers to form lower viscosity solutions was used to the advantage of the formulation chemist.

Surface modifications of dendrimers have been used as molecular-carrying systems. For example, dendrimers containing at least one free amino group have been used to carry anti-acne agents in a patent filed by Revlon consumer products [249]. A keratolytic or anti-acne agent was complexed with a carrying molecule such as a dendrimer containing free amino groups to obtain cosmetically acceptable formulations for treatment of acne vulgaris. In another example of a dendrimer-molecule conjugate system, coupling of aminobutadiene with an amine-rich dendritic molecule provided advantageous UV-absorbing capabilities to the final product [250].

This high-molecular-weight dendrimer-aminobutadiene-complexed molecule allowed ease in formulating a clear sunscreen composition without developing high-viscosity gels, which in turn provided ease of application to the skin. Because of the high molecular weight of the resulting molecule, it was nonpenetrating into the skin, which would minimize risk of irritation or sensitization reactions while acting as a UV-light absorber when applied on the skin's surface. In another application, amine-terminated cationic dendrimers have been used in personal-care cleansing compositions as mildness agents [251].

Linear cationic polymers used as mildness agents usually precipitate in the presence of anionic surfactants, which reduce their lathering, skin conditioning, or cleansing effects. Dendrimers, on the other hand, are capable of interacting favorably and can bind with anionic surfactants in the composition to remain dispersed in salt solutions. This interaction of cationic dendrimers with skin-irritating anionic surfactants could potentially be used by the personal care chemist for reducing the skin irritation potential of cosmetic formulations containing harsh anionic surfactants.

US patent 6,001,342 described the use of dendrimers containing terminal amine groups such as polyamidoamines (Starburst, Starpharma) in antiperspirant deodorant compositions to reduce underarm odors [252]. Some of the selected dendrimers were found to have odor-absorbing properties and were claimed as deodorant active agents. These dendrimers could be formulated in water-based compositions in appreciable amounts and were found to be nontoxic or nonirritating.

Novel self-tanning cosmetic compositions described in US Patent 6,399,048 contain amine-terminal group dendrimers in addition to a tanning agent [253]. The dendrimer-containing composition was shown to have improved efficacy and self-tanning activity on application to skin. Dendrimer-containing compositions in this case were shown to increase the intensity and quality of skin coloration produced, as well as providing a shade that was closer to a natural tan. As shown in various examples of dendrimer application, the rich functional surface groups and the viscosity characteristics of dendrimers have been used to add unique claims and product differentiation to personal-care products.

CONCLUSION

The objective of this review was to summarize the unique properties and advantages that dendrimers offer along with its application in field of drug delivery, diagnosis and therapy.

Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Although the application of dendrimers in the field of drug, gene, and vaccine delivery is in its infancy, dendrimers offer several attractive features, including the control one has over the primary nature of the system. They provide a platform for the attachment of drugs or genes and their release through several mechanisms.

The main conclusion is that the high level of control over the architecture of dendrimer, their shape, branching length and density, their surface functionality and interior void space (porosity) and so on makes dendrimer ideal carriers for the various applications like drug delivery, therapeutic and diagnostic agent. Poor solubility, bioavailability and permeability biocompatibility and toxicity can be overcome by use it.

The high density of surface groups allows attachment of targeting groups as well as groups that modify the solution behaviour or toxicity of dendrimers. Bioactive agents might be encapsulated into the interior, physically adsorbed or chemically attached to the dendrimer surface, with many options for tailoring vector properties to the specific needs of the active material and its therapeutic applications.

Furthermore, the ability to select nanoscale-sized vectors with mathematically determined numbers of surface groups and welldefined interior void space allows systematic size adjustments to determine excretionary pathwayswhile producing optimal ratios of targeting moieties, therapy and surface groups required in combination with desired solution behavior, excretionary pathway and acceptable toxicity margins. Finally, certain anionic surface-modified dendrimers are proving to function as safe and effective topical nanopharmaceuticals against HIV and genital herpes.

Hopefully, this review of dendrimer-based medical applications clearly illustrates the potential of this new ‘fourth architectural class of polymers’ and reaffirms an even higher level of optimism for the future role of dendrimers in the drug delivery, diagnosis and therapy.

FUTURE PROSPECTS

Dendrimeric polymers are very important and convenient for drugs delivery, diagnosis and therapy. In order to be effective, dendrimer-based products should be based on scientific evidence for their usefulness and must be easier to translate from laboratory to the clinic, in other words be quality-controlable, cost-effective and sustainable.

Literature review of biomedical applications of the dendrimers clearly illustrate the potential of this new fourth architectural class of polymers and substantiate the high optimism for the future of dendrimers in drug delivery,

diagnosis and therapy. Scientists have explored the use of dendrimers for various applications in oral, transdermal, ophthalmic, and gene delivery. Although dendrimer drug delivery requires attention to certain manufacturing and biological considerations to be successful.

Besides drug delivery, dendrimers have been found to have a great emphasis in gene delivery, boron neutron capture therapy, PDT and as magnetic resonance imaging contrast agents. The use of dendrimers in the clinic has still not reached the success of linear polymers and several applications remain to be explored for its industrial as well as biomedical applications. With improved synthesis, further understandings of their unique characteristics and recognition of new applications, dendrimers will become promising candidates for further exploitation in drug discovery and clinical applications. Boosting of commercial applications of dendrimer technology will provide strength for its usefulness in future.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper

Abbreviations: 2-AS, 12-(9-anthroyloxy) stearic acid; 2-D, two-dimensional; 3-D, three-dimensional; 3-TC, lamivudine; Ac, acetylated; AChE, acetylcholinesterase; AF, alexaFluor; AFM, atomic force microscopy; ATRP, atom transfer radical polymerization; b-FGF, basic fibroblast growth factor; BAPTA-AM, 1,2-bis-(o-aminophenoxy) ethane-N,N,N',N',-tetraacetic acid-acetoxymethyl ester; ˇ-CD, ˇ-cyclodextrin; BBB, blood brain barrier; BMVEC, brain micro-vessel endothelial cells; BNTC, boron neutron capture therapy; BSA, bovine serum albumin; CLB, chlorambucil; CED, convection enhanced delivery; CMCht, carboxymethylchitosan; CMCht/PAMAM, carboxymethylchitosan/poly (amidoamine); DCC, dicyclohexylcarbodiimide; Dex, dexamethasone; DDS, drug delivery system; di-BOC, di-tert-butyl dicarbonate; DOPE, 1,2-dioleyl-3-phosphatidylethanolamine; DOTAP, N-(1-(2,3-dio-leoyloxy) propyl)-N,N,N-trimethyl ammonium methylsulfate; Dox, doxorubicin; EBV, Epstein Barr virus; ECM, extracellular matrix; EG, ethylene glycol; EGF, epidermal growth factor; EGFP, green fluorescent protein; ENFET, enzyme field-effect transistor; EPR, electron paramagnetic resonance; FA, folic acid; FITC, fluorescein isothiocyanate; G, generation number; GAGs, glycosaminoglycans; GLUT 1, glucose transporter; GOX, glucose oxidase; HA, Hyaluronic acid; HAp, hydroxyapatite; HAS, human serum albumin; HBP, hyperbranched polymer; HER-2, human growth receptor; HMGB1, high mobility group box 1 plasmid; HSGP, heparin or heparan sulfate proteoglycan; i.p., intraperitoneal; i.t., intratumoral; LCST, lower critical solution temperature; LH, light-harvesting; MA, methacrylate; MAPs, multiple antigen peptides; Man, mannose; Mn, number-average molecular weight; Mo/Mac, monocyte/macrophages; MPPI, poly(propyleneimine); MRI, magnetic resonance imaging; MS, multiple sclerosis; Mw,weight-average molecular weight,Mw/Mn polydispersity index; NaHA, sodium hyaluronate;NMR,nuclear magnetic resonance; OEI, oligoethylenimine; OG, oregon green; ONs, antisense oligonucleotides; PAMAM, poly(amidoamine); PAH, p-aminohippuric acid; PCI, photochemical-internalization; PDMA, poly(N,N-dimethylaminoethyl methacrylate); PEG-DA, poly(ethylene glycol)-dialdehyde; PEI, poly(ethyleneimine); PEPE, polyether-copolyester; PETIM, poly(propyl ether imine); PLGSA, poly(glycerol-succinic acid); PLL, poly-(l-lysine); PNIPAAM, poly(N-isopropylacrylamide); PP, primaquine phosphate; PPI, poly(propyleneimine); PrPSc, protease-resistant isoform of the prion protein; PSMA, prostrate specific membrane antigen; PTX, paclitaxel; RAFT, reversible addition-fragmentation transfer; RGD, Arg-Gly-Asp peptides; ROS, reactive oxygen species; SA, sulfasalazine; SEM, scanning electron microscopy; shRNA, small hairpin RNA; t-BOC, N-tert-butoxycarbonyl; TE, tissue engineering; ThT, thioflavin T; TIMP, tissue inhibitors of metalloproteinases; TMA-DPH, 1 (trimethylammoniumphenyl)-6-phenyl-1,3,5 hexatriene p-toluenesulfonate; VEGF, vascular endothelial growth factor.

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