



DENDRIMER: A COMPLETE DRUG CARRIER

B.Pavan Kumar*, I.SarathChandiran, B.Bhavya, Sravanthi.U, Sindhuri.M

***Depart. of Pharmaceutics, Gokula Krishna College of Pharmacy, Sullurpet–524121, Nellore, AP**

ABSTRACT

Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. As a result of their unique behaviour; dendrimer is suitable for a wide range of biomedical and industrial applications. The unique architecture design of dendrimers, high degree of branching, multivalency, globular architecture and well defined molecular weight distinguishes these structures as unique and optimum nanocarriers in medical applications, such as drug delivery, gene transfection, tumor therapy, diagnostics etc. Micro/Nanoparticle drug-delivery system is the popular one and able to increase the selectivity and stability of therapeutic agents. The bioactive agents can be easily encapsulated into the interior of dendrimers (or) chemically attached i.e. conjugated or physically absorbed onto the dendrimer surface, serving the desired properties of the carrier to the specific needs of the active material and its therapeutic applications. In addition to supplying a multivalent backbone for drug attachment dendrimers also provide access to various new polymer architecture that are potentially relevant to drug delivery applications.

Keywords: Dendrimer, Polymeric drug carrier, Microparticulate/Nano particulate, drug delivery systems

INTRODUCTION

Dendrimers are the new artificial macromolecules which are characterized by hyperbranched, monodisperse 3D structure that provides a high degree of surface functionality and versatility. Dendrimers have often been referred to as the “Polymers of the 21st century” [1,2]. Since dendrimers are synthesized from branched monomer units in a stepwise manner, it is possible to conduct a precise control on molecule size, shape, dimension, density, polarity, flexibility, and solubility by choosing different building/branching units and surface functional groups. Moreover, they can use small organic molecules and polymers as structural components, and thus acquire special physical and chemical properties.

Up to now, dendrimers have been widely applied in many fields, such as supramolecular chemistry or host–guest chemistry, electrochemistry, and photochemistry, nanoparticle synthesis, pollution management, dye decolorization, preparation of monomolecular membranes, curing of epoxy resins, catalysis, drug delivery, and gene transfection. Among them, the use of dendrimers in delivery systems has deserved more attentions in recent years. Recently, more research focused on the application of dendrimers in biomedical fields. This review highlights the dendrimer structure and its components, synthesis, types, mechanisms of drug delivery, properties, effect of various factors on properties, characterization as well as recent studies on the applications of dendrimers [2].

STRUCTURE

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure as shown in fig:1. As the process repeats, successive layers are added and the sphere can be expanded to the size required by the investigator. Dendrimers possess three distinguished architectural compounds, namely

1. An initial core.
2. Interior layers (generations) composed of repeating units, radically attached to the interior core.
3. Exterior (terminal functionality) attached to the outermost interior generations.

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the 'starburst effect' [3,4].

COMPONENTS OF A DENDRIMER STRUCTURE GENERATION

It is a hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points). The number of focal points when going from the core towards the dendrimer surface is the generation number i.e., a dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer shown in fig:2. It is abbreviated as G5-dendrimer, e.g. a 5th generation polypropylene imine is abbreviated to a "G5-PPI-" dendrimer. The core part of the dendrimer is sometimes denoted "G0" (generation 'zero'). Intermediates during dendrimer synthesis are sometimes denoted half generations.

SHELL

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

PINCER

In dendrimers, the outer shell consists of a varying number of pincers created by the last focal point before reaching the dendrimer surface. In PPI and PAMAM dendrimers the number of pincers is half the number of

surface groups (because in these dendrimers the chain divides into two chains in each focal point).

END GROUP

It is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "amino-terminated dendrimers" [3].

Dendrimer Synthesis

Three fundamentally different methods have been developed for stepwise synthesis of dendritic polymers.

Divergent growth method

This type of synthesis involves addition of branching monomer units repeatedly on to produce a dendrimer of desired generation number.

Starting from a reactive core, a generation is grown, and then the new periphery of the molecule is activated for reaction with more monomers as shown in fig:3. The two steps can be repeated. The divergent approach is successful for the production of large quantities of dendrimers since, in each generation-adding step, the molar mass of the dendrimer is doubled.

Convergent growth method

The 'convergent' approach was developed as a response to the weaknesses of divergent synthesis. Convergent growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer as shown in fig:4. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step.

Double Exponential' and 'Mixed' Growth

The most recent fundamental breakthrough in the practice of dendrimer synthesis has come with the concept and implications of 'double exponential' growth. Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB₂ monomer with orthogonal protecting groups for the A and B functionalities. This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material. It is shown in fig:5. These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. The strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. The double exponential methodology provides a

means whereby a dendritic fragment can be extended in either the convergent or the divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings [2,5].

TYPES OF DENDRIMERS

PAMAM Dendrimers

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10^9 (a molecular weight of over 9, 30,000 g/mol) have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, usually as methanol solutions. *Starburst dendrimers* is applied as a trademark name for a subclass of PAMAM dendrimers based on a tris-aminoethylene-imine core. The name refers to the starlike pattern observed when looking at the structure of the high generation dendrimers of this type in two dimensions.

PAMAMOS Dendrimers

Radially layered poly (amidoamine- organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" describing the propylamine spacer moieties is the oldest known dendrimer type developed initially by Vögtle. These dendrimers are generally poly-alkyl amines having primary amines as end groups. The dendrimer interior consist of numerous tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine), which closely resembles the PPI abbreviation. In addition, these dendrimers are also sometimes denoted "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

TectoDendrimer

These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design)

to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

Multilingual Dendrimers

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

Chiral Dendrimers:

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

Hybrid Dendrimers Linear Polymers

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

Amphiphilic Dendrimers

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

Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

Multiple Antigen Peptide Dendrimers

It is a dendron-like molecular construct based upon a poly-lysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, e.g. vaccine and diagnostic research.

Fréchet-Type Dendrimers

It is a more recent type of dendrimer developed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalisation, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media [1,4].

MECHANISMS OF DRUG DELIVERY

Dendrimers are particularly attractive as they offer a high drug-loading capacity. Different release mechanisms have been explored, and they can be broadly subdivided into three types: simple encapsulation, electrostatic interaction and covalent conjugation.

Simple Encapsulation

The ellipsoidal or spheroidal shape, empty internal cavities, and open nature architecture of dendrimers make it possible to directly encapsulate guest molecules into the macromolecule interior. These empty internal cavities usually have hydrophobic properties, which make it suitable to interact with poorly-soluble drugs through hydrophobic interactions. In addition, there are nitrogen or oxygen atoms in these internal cavities, which can interact with the drug molecules by hydrogen bond formation. In view of these specific properties, the relationship between the internal cavities of dendrimers and drug molecules may involve physical encapsulation, hydrophobic interaction, or hydrogen bonding.

Electrostatic Interaction

The high density of functional groups (such as amine groups and carboxyl groups) on the surface of dendrimers may be expected to have potential applications in enhancing the solubility of hydrophobic drugs by electrostatic interaction. For example G3 PAMAM dendrimer with an ammonia core has a much higher amino group density when compared with classical linear polymers (a G3 PAMAM dendrimer has 1.24×10^{-4} amine moieties per unit volume (cubic Angstrom) in contrast to the 1.58×10^{-6} amine moieties per unit volume of a conventional star polymer). In recent years, nonsteroidal anti-inflammatory drugs with carboxyl groups, including ibuprofen, ketoprofen, diflunisal, naproxen, and indomethacin, have been widely complexed with dendrimers by electrostatic interactions. Studies on other drugs, such as some anti cancer drugs and anti-bacterial drugs, have also been reported. The common property of these drug molecules is that they are weakly acidic drugs with carboxyl groups in the molecules [1,2].

Covalent Conjugation

The presence of large numbers of functional groups on the surface of dendrimers makes them suitable for the covalent conjugation of numerous drugs with relevant functional groups. In this case, the drug is covalently bound to dendrimers, and its release occurs via chemical or enzymatic cleavage of hydrolytically labile bonds. The encapsulation of drug molecules within hydrophobic cavities or absorption of drugs to the surface of dendrimers via electrostatic interactions preserves the chemical integrity and pharmacological properties of drug molecules, while covalent attachment of drugs to the surface groups of dendrimers through chemical bonds offers the opportunity for a better control over drug release than that can be achieved by simple encapsulation/electrostatic interaction of drugs into/with the dendrimers.

Covalent conjugation allows tissue targeting and controlled delivery as the drug-dendrimer conjugates diffuse slower than the free drug in the body and might be absorbed

in specific interfaces. Naturally, a problem may arise as a consequence of coupling large numbers of drugs to the dendrimer surface by covalent conjugation, that is, the insolubility of the resultant product. This problem often can be resolved through the concomitant attachment of short PEG chains. Conjugates of PAMAM dendrimers with cisplatin, a potent anticancer drug with non-specific toxicity and poor water solubility. The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors [6].

PROPERTIES OF DENDRIMERS [2,5]

Monodispersity

Distinct from traditional linear polymers, dendrimers synthesized step-by-step have well-organized structures with a very low polydispersity. It is due to the precise synthesis and purification strategy in the preparing process. Up to now, the monodisperse property of dendrimers has already been extensively characterized by high performance liquid chromatography (HPLC), size exclusion chromatography (SEC), mass spectrometry (MS), gel electrophoresis, and transmission electron microscopy (TEM). It should be noted that there exists inherent structural defects when synthesizing high-generation dendrimers. The reasons include incomplete reactions and steric resistance, which cause the missing of repeating units, intramolecular cyclization, dimer formation and retro-Michael reaction in dendrimers. However, MS results show that the molecular weight distributions of these high-generation dendrimers still remain very narrow (polydispersity < 1.05). That is why Tomalia, who firstly reported the synthesis of PAMAM dendrimers in 1984, said, "Dendrimers synthesized by convergent method are probably the most precise synthetic macromolecules today."

Nanoscale Dimensions and Shapes

Dendrimers have nanoscale dimensions due to their well-organized synthesis strategy and size controllable properties. Within the PAMAM dendrimer family, when they grow from generation 1–10, the diameter of dendrimers with an ethylenediamine core increases from 1.1 to 12.4 nm. The shape of dendrimers may vary with their generations. The PAMAM dendrimers of low generation (G0–G3) with an ethylenediamine core and without interior characteristics have ellipsoidal shapes, whereas the PAMAM dendrimers of high-generation (G4–G10) with well-defined cavities have roughly spherical shapes [2,5].

Defined architecture, size and shape control

Dendrimers branch out in a highly predictable fashion to form amplified three-dimensional structures with highly ordered architectures. This property is relevant for applications such as protein modeling or catalysis. Size control is also important in therapeutic applications, as different molecular sizes exhibit different pharmacokinetics.

Other dendritic polymers such as *dendronised* polymers or hybrid linear-dendritic structures can have more potential than pure dendrimers for certain medical applications, but a key requirement for biological applications will be the ability to deliver a pure product; hence hybrid dendritic structures for such applications will generally start with dendrimer construction followed by the hybridization phase. The shape persistence of dendrimers is very important, as it allows the defined placement of functions not only on the dendrimer surface but also inside the dendritic scaffold. This is of crucial importance for several applications, e.g. in sensing. Furthermore, stiff dendritic architectures possess defined pores or voids. This is a prerequisite for defined interactions between the dendrimer and incorporated guest molecules.

Solubility and Reactivity

The solubility of dendrimers is determined by the surface functional groups, dendrimer generation, repeated units, and even the core. Dendrimers were reported to possess perfect solubility in a large number of solvents. Their high solubility in organic solvents leads to rapid dissolution and provides various approaches to characterize their structures. Also, high water-solubility ensures their applications as solubility enhancers for hydrophobic guest molecules. On the other hand, high density of surface functional groups ($-NH_2$, $-COOH$, $-OH$) in PAMAM dendrimers may be expected to conjugate with a series of bioactive molecules. These surface-modified dendrimers with different functions provide us with new nanodevice design strategies. Overall, high solubility and reactivity make dendrimers suitable as a platform in biomedical fields [7].

Dynamic Structures

The conformation of dendrimers depends not only on their generation but also the environment where they exist. Welch and Muthukumar, using Monte Carlo simulations, reported that the conformations of dendrimers were tunable from that of the dense core to that of the dense shell by manipulation of the salt concentration or pH in aqueous solutions. It is proposed therefore that the structures of dendrimers in solutions are quite dynamic. However, it is generally accepted that higher generation dendrimers still keep their roughly globular shapes in solutions.

Encapsulating guest molecules

Because of their globular shape and the presence of internal cavities, it is possible to encapsulate guest molecules in the macromolecule interior. Meijer and coworkers trapped small molecules like rose bengal or *p*-nitrobenzoic acid inside the 'dendritic box' of poly(propylene imine) dendrimer with 64 branches on the periphery. Then a shell was formed on the surface of the dendrimer by reacting with

the terminal amines of an amino acid (L-phenylalanine) and guest molecules were stably encapsulated inside the box [6].

Polyvalency

The outer shell of a dendrimer admits functionalisation fairly easy, allowing multiple functionalities to be added. Polyvalency is useful as it provides versatile functionalisation; it is also extremely important to produce multiple interactions with biological receptor sites, for example, in the design of antiviral therapeutic agents. Using dendrimers as a scaffold to present multiple copies of a surface group or groups, new biological activities are uncovered with unique pharmacokinetics. Different ligands can be coupled to dendrimers to use them as transfection reagent, e.g., ligands recognizing only the surface of a certain cell type combined with ligands that facilitate the escape from the *endosome*. Functionalization of the periphery can also result in copolymers with interesting properties, such as viscosity, stability, etc., and dendrimer fillers are already fairly widely used in composites and other materials to modify such properties. Dendrimer properties can be easily tuned by modifying the end groups (e.g. changing the end groups on a same skeleton induces solubility in organic solvents, in CFC or in water).

Loading capacity (molecular container property)

In addition to carrying materials on their surface, the internal cavities of dendritic structures can be used to carry and/or store a wide range of metals, organic, or inorganic molecules by encapsulation and absorption. The appropriate type (and degree) of functionalisation will result in the desired loading capacity. This property makes dendrimers very suitable as drug delivery vehicles and also appropriate for obtaining electro-optic or magnetic devices. It also allows the use of dendrimers to store, for example, nanoparticles of metal and to prevent precipitation, allowing for the creation of dispersions of what some have called 'nanoreactors'. The possibility of loading dyes could lead to novel ways of labeling and has been used to color polymers with a dendrimer additive (dendrimers can mix and bond better than the raw dye filler).

Biocompatibility / low toxicity

Some dendrimer systems display very low toxicity levels – with dendrimers carrying anionic groups being less toxic than those carrying cationic groups. Dendrimers commonly show also negligible or very low immunogenic response when injected or used topically. These properties make them highly suitable for drug delivery and biolabeling. In this sense, high biocompatibility is crucial both for preventing toxic reaction and for seeking biodegradability options. Dendrimers can, of course, be made from biomaterials themselves, with DNA being a popular choice. Dendritic polymers have great potential in various kinds of

therapies, especially given their ability to be designed for biological specificity, therefore their biocompatibility and lack of toxicity is important. However, not all dendrimers are biocompatible nor show low toxicities.

Transfection properties

The high diversity of chemical structures possible in dendritic architectures enables the design of selected macromolecules that are able to pass through membranes [7].

Comparison of Properties of Dendrimer and linear polymers

The comparison of properties of dendrimers with that of linear polymers is given in detail in table:1.

EFFECT OF VARIOUS FACTORS ON THE PROPERTIES OF DENDRIMERS

Effect Of pH

Amino-terminated PPI and PAMAM dendrimers have basic surface groups as well as a basic interior. For these types of dendrimers with interiors containing tertiary amines, the low pH region generally leads to extended conformations due to electrostatic repulsion between the positively charged ammonium groups. Applying molecular dynamics to predict the structural behaviour of PAMAM dendrimers as a function of pH show that the dendrimer has an extended conformation, based on a highly ordered structure at low pH (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 contracts 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 (Figure 6).

When looking at the pH-dependent conformational changes of **PPI dendrimers having acidic (carboxylic acid) end-groups**, the picture is somewhat different compared to what is observed for their amino-terminated counterparts (Figure 6). Small angle neutron scattering (SANS) and NMR measurements of self-diffusion coefficients at different pH values show that at pH 2 the dendrimer core has the most extended conformation due to the electrostatic repulsion between the positively charged protonated tertiary amines, leading to a large radius of the core, whereas the dendrimer reaches its minimum radius at

pH 6, where the amount of positively charged amines equals the amount of negatively charged carboxylic groups (isoelectric point) resulting in a "dense core" conformation more subjective to back-folding. Thus, at pH 6 some degree of back-folding occurs as a result of attractive interactions between the negatively charged surface carboxy-groups and the positively charged tertiary amines in the inner shells of the dendrimer. At pH 11 the electrostatic repulsion between the negative charged forces the surface groups apart to give a more extended conformation with a highly expanded surface area (Figure 7).

Effect of Solvent

The ability of the solvent to solvate the dendrimer structure is a very important parameter when investigating the conformational state of a dendrimer. Dendrimers of all generations generally experience a larger extent of back-folding with decreasing solvent quality, *i.e.* decreasing 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 conclude that a nonpolar solvent like benzene, poorly solvates the dendrons favoring intramolecular interactions between the dendrimer segments and back-folding. However, 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 (good) solvents solvate the dendrimer arms and induce a higher molecular density on the dendrimer surface. Back-folding of the polar surface groups may expose the more hydrophobic dendrimer parts to the surroundings leading to a decreased surface polarity of the back-folded dendrimer. (Figure:8)

Effect of Salt

High ionic strength (high concentration of salts) has a strong effect on charged PPI dendrimers and favors a contracted conformation of dendrimers, with a high degree of back-folding somewhat similar to what is observed upon increasing pH or poor 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 (Figure 9).

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. (Figure 10)

METHODS FOR CHARACTERIZATION OF DENDRITIC POLYMER

The earliest work on dendrimer characterization was concerned with aspects of the organic chemistry. Since near 100 % conversion and near perfect removal of excess reactants is required for making pure dendrimer, common methods of spectroscopy and chromatography can be used to verify the structure. In a wide variety of dendrimer chemistries, nearly perfect structures have been produced, at least for earlier generations where the techniques are more quantitative.

The development of mass spectroscopic techniques such as MALDI and electrospray mass spectrometry has allowed the absolute determination of dendrimer perfection. Mass spectrometric results on dendrimers demonstrate the extreme sensitivity of the technique and the uniformity of the molecular mass.

Scattering techniques measure the radius of gyration (R_g) of dendrimers, which is an average of the spatial distribution of all of the units. Transmission electron microscopy (TEM) has been used to image individual dendritic molecules, usually the larger generations. Recently atomic force microscopy (AFM) has also been used to image dendritic molecules.

Following methods can be used for characterization of dendritic polymers.

1.Spectroscopy and spectrometry methods like Nuclear Magnetic Resonance (NMR), Infra-red (IR) and Raman, Ultra-violet-visible (UV-VIS), Fluorescence, Chirality, Optical rotation, Circular dichroism (CD), X-ray diffraction, and Mass spectrometry

2.Scattering techniques like Small angle X-ray scattering (SAXS), Small angle neutron scattering (SANS), and Laser light scattering (LLS)

3.Electrical techniques like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis

4.Size exclusion chromatography (SEC)

5.Microscopy like Transmission electron microscopy, Scanning electron microscopy and atomic force microscopy

6.Rheology, physical properties like intrinsic viscosity, Differential Scanning Calorimetry (DSC), and Dielectric spectroscopy (DS)

7.Miscellaneous like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc.

APPLICATIONS OF DENDRIMERS

The dendrimers have wide range of applications not only to the pharmaceutical field but also to the other fields. Various applications of dendrimers are shown in figure 11.

PHARMACEUTICAL AND BIOMEDICAL APPLICATIONS

The formation of particulate systems with well-defined sizes and shapes is of eminent interest in certain medical applications such as drug delivery, gene transfection, and imaging. The high level of control possible over the architectural design of dendrimers; their size, shape, branching length/density, and their surface functionality, clearly distinguishes these structures as unique and optimum carriers in those applications. The bioactive agents may be encapsulated into the interior of the dendrimers or chemically attached/physically adsorbed onto the dendrimer surface, with the option of tailoring the carrier to the specific needs of the active material and its therapeutic applications. In this regard, the high density of exo-presented surface groups allows attachment of targeting groups or functionality that may modify the solution behavior or toxicity of dendrimers. Quite remarkably, modified dendrimers have been shown to act as nano-drugs against tumors, bacteria, and viruses. Recent successes in simplifying and optimizing the synthesis of dendrimers such as the 'lego' and 'click' approaches, provide a large variety of structures while at the same time reducing the cost of their production.

Targeted and controlled release drug delivery

An ideal drug delivery system possesses two elements: the ability to target and controlled release. Targeting will ensure a high efficiency of the drug and possibly reduces side effects of the drug. Dendrimers have unique characteristics including monodispersity and modifiable surface functionality, along with highly defined size and structure. This makes these polymers attractive candidates as carriers in drug delivery applications. Drug delivery can be achieved by coupling a drug to polymer through one of two approaches. Hydrophobic drugs can be complexed within the hydrophobic dendrimer interior to make them water-soluble or drugs can be covalently coupled onto the surface of the dendrimer. The reduction or even prevention of side effects can also be achieved by controlled release. Modified dendrimers can be used to carry drug molecules to a specific location and release them in a controlled way. Methods to achieve controlled

release include chemical or enzymatic reaction, diffusion through a matrix, or solvent activation.

Solubility Enhancement

Poor solubility and hydrophobicity of drugs/bioactives limit their possible applications in drug delivery and formulation development. Apart from conventional methods of solubility enhancement, there are some novel methods which can be used in solubilization. Dendrimers represent a novel type of polymeric material that has generated much interest in solubility enhancement due to their unique structure and properties. Dendrimer-mediated solubility enhancement mainly depends on factors such as generation size, dendrimer concentration, pH, core, temperature, and terminal functionality. Dendrimers having a hydrophobic core and a hydrophilic surface layer have been termed as unimolecular micelles. Unlike traditional micelles, dendrimers do not have a critical micelle concentration. This characteristic offers the opportunity to solubilize poorly soluble drugs by encapsulating them within the dendritic structure at all concentrations of dendrimer. A hydrophilic–hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-fluorouracil, a water-soluble anti-tumor drug. After phospholipid coating of the dendrimer–fatty-acid macromolecule, oral bioavailability in rats of 5-fluorouracil was nearly twice the level of free 5-fluorouracil. Dendrimer-based carriers could offer the opportunity to enhance the oral bioavailability of problematic drugs. Propranolol, conjugated to surface-modified G3 PAMAM dendrimer, the solubility of propranolol increased by over two orders of magnitude. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

Delivery of Anticancer Drugs by Dendrimers and Dendritic Polymers

The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h). In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. Combined, these factors lead to the selective accumulation of macromolecules in tumor tissue – a phenomenon termed the ‘Enhanced Permeation and Retention’ (EPR) effect. Therefore, the anticancer drug doxorubicin was covalently bound to this carrier via an acid-labile hydrazone linkage. The cytotoxicity of doxorubicin was significantly reduced (80–98%), and the drug was successfully taken up by several cancer cell lines. The encapsulation behavior of these compounds for the anticancer drugs adriamycin and methotrexate was studied. The highest encapsulation efficiency, with on average 6.5 adriamycin molecules and 26 methotrexate molecules per dendrimer, was found for the G = 4 PAMAM terminated with PEG2000 chains. The anticancer drug 5-fluorouracil encapsulated into G = 4

PAMAM dendrimers with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, and reduced release rate and hemolytic toxicity compared to the non-PEGylated dendrimer. In contrast, up to 24 drug molecules were encapsulated into the hyper branched polyol. The drug was successfully transported into lung epithelial carcinoma cells by the dendrimers. Recent studies using Caco-2 cell lines have indicated that low generation PAMAM dendrimers cross cell membranes presumably through a combination of two processes, i.e., paracellular transport and adsorptive endocytosis, while cell efflux systems have a minor effect. (Figure:12)

Cellular Delivery Using Dendrimer Carriers

Kannan et al. studied the dynamics of cellular entry into A549 human lung epithelial carcinoma cells of a range of PAMAM dendrimers (G4-NH₂, G3-NH₂, G4-OH, PEGylated G3 [G3-PEG]) and a hyper branched polymer (polyol). G4-NH₂ and G4-OH entered cells more rapidly than did G3-NH₂, polyol or G3-PEG. It was suggested that the rapid entry of G4-NH₂ might be a result of the cationic nature of the amine surface groups, which may interact electrostatically with negatively charged epithelial cells and enter via fluid phase pinocytosis. The lower rate of cellular entry of G3-NH₂ compared with G4-NH₂ may be a result of fewer surface charges on the G3-NH₂ dendrimer. Because polyol and G3-PEG do not have cationic surface groups, their cellular entry may result from non-specific adsorption to the cell membrane and subsequent endocytosis. Dendrimer–ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus >3 hr), suggesting that dendrimers can efficiently carry the complexed drug inside cells. PAMAM dendrimers were surface-engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

Dendrimers as Nano-Drugs

Poly (lysine) dendrimers modified with sulfonated naphthyl groups have been found to be useful as antiviral drugs against the herpes simplex virus and potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs). In earlier studies, it was found that PAMAM dendrimers covalently modified with naphthylsulfonate residues on the surface also exhibited antiviral activity against HIV. This dendrimer-based nano-drug inhibited early stage virus/cell adsorption and later stage viral replication by interfering with reverse transcriptase and/or integrase enzyme activities. PPI dendrimers with tertiary alkyl ammonium groups attached to the surface have been shown to be potent antibacterial biocides against Gram positive and Gram negative bacteria. Poly (lysine) dendrimers with mannosyl surface groups are effective inhibitors of the adhesion of *E. coli* to horse blood cells in a haemagglutination assay, making these structures promising antibacterial agents. Chitosan–dendrimer hybrids have been found to be useful as antibacterial agents,

carriers in drug delivery systems, and in other biomedical applications.

Dendrimers in Gene Transfection

Dendrimers can act as **vectors, in gene therapy**. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and, ultimately, into the cell nucleus. A transfection reagent called SuperFect™ consisting of activated dendrimers is commercially available. Activated dendrimers can carry a larger amount of genetic material than viruses. SuperFect–DNA complexes are characterized by high stability and provide more efficient transport of DNA into the nucleus than liposomes. The high transfection efficiency of dendrimers may not only be due to their well-defined shape but may also be caused by the low pK of the amines (3.9 and 6.9). The low pK permit the dendrimer to buffer the pH change in the endosomal Compartment. PAMAM dendrimers functionalized with cyclodextrin showed luciferase gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and cyclodextrin. It should be noted that dendrimers of high structural flexibility and partially degraded high-generation dendrimers (i.e., hyper branched architectures) appear to be better suited for certain gene delivery operations than intact high-generation symmetrical dendrimers [3,4,7]. (Figure 13)

Transdermal drug delivery

PAMAM dendrimers enhanced the bioavailability of indomethacin in transdermal delivery applications. Wang *et al* reported the utilization of polyhydroxyalkanoate and G 3 PAMAM dendrimers as Transdermal drug delivery (TDDS). Cheng *et al.*, investigated TDDS for anti-inflammatory drugs and concluded that the bioavailability of anti-inflammatory drugs was increased; it may be due to the facilitated skin penetration.

Ocular drug delivery

Vandamme and Broberck have reported the development of ophthalmic vehicles in ocular drug delivery using PAMAM dendrimers for pilocarpine nitrate. They found that there is more ocular residence time and significantly increased bioavailability by using PAMAM dendrimers.

Nano-devices

The characteristic non toxicity of PAMAM dendrimers to biological systems makes their biocompatibility considerably greater than that of many other materials currently researched for use as controlled, chemotherapeutic drug delivery systems. The

multifunctionality and biocompatibility of dendrimer-based nanodevices are crucial for the development of targeted drug delivery technology. Multifunctional cancer therapeutic nanodevices have been designed and synthesized using the PAMAM dendrimer as a carrier. Partial acetylation of amine-terminated PAMAM dendrimer can be used to neutralize a fraction of the primary amino groups, provide enhanced solubility of the dendrimer during the conjugation reaction of fluorescein isothiocyanate (FITC) in dimethyl sulfoxide (DMSO), and prevent nonspecific targeting interactions (*in vitro* and *in vivo*) during delivery.

Dendrimers in Photodynamic Therapy:

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes. Photo sensitive dyes have been incorporated into dendrimers and utilized in PDT devices. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue. The possibility of improving the properties of dendrimers through appropriate unfunctionalization of their periphery makes dendrimers promising carriers for photosensitizers. ALA is a natural precursor of the photosensitizer protoporphyrin IX (PIX), and its administration is known to increase cellular concentrations of PIX.

Multivalent Diagnostics for MRI

The applications of gadolinium chelating poly (propylene imine) dendrimers for Magnetic Resonance Imaging (MRI) are possible. Gadolinium-based MRI contrast agents can be effective at an approximately 100-fold lower concentration of Gadolinium ions in comparison to the concentration of Iodine atoms required for CT imaging. Therefore, a number of dendrimer based macromolecular MRI contrast agents of various sizes and properties prepared employing relatively simple chemistry are readily available that can provide sufficient contrast enhancement for various applications. Molecules up to 20 nm in diameter behave differently in the body depending on their size. Even if these molecules possess similar chemical properties, small changes in size can greatly impact their pharmacokinetics. Changes in molecular size up to 15 nm in diameter altered permeability across the vascular wall, excretion route, and recognition by the reticuloendothelial system. Smaller sized polyamidoamine (PAMAM) dendrimer-based contrast agents, i.e., less than 3 nm in diameter, easily “leak” across the vascular wall resulting in rapid perfusion throughout the body. Contrast agents of 3-6 nm in diameter were quickly excreted through the kidney indicating these agents to be potentially suitable as functional renal contrast agents. Contrast agents 7-12 nm in diameter were retained in circulation and were better suited for use as blood

pool contrast agents. Hydrophobic variants of contrast agents formed with polypropyleniminediaminobutanedendrimer cores quickly accumulated in the liver and potentially have use as liver contrast agents. Larger hydrophilic agents have suitable characteristics for lymphatic imaging. Finally, contrast agents conjugated with either monoclonal antibodies or with avidin are able to function as tumor-specific contrast agents and might also be employed as either gadolinium neutron capture therapy or in conjunction with radioimmunotherapy.

Sensors

Due to their organized structure ease of modification, and strong adsorption behavior to a variety of substrates, PAMAM dendrimers can be used to produce monolayers or stacked film layers, which can be used as sensors to detect hazardous chemical vapors. A hydrogen peroxide biosensor based on nano-Au/PAMAM dendrimer is also reported.

Molecular Weight and Size Standards

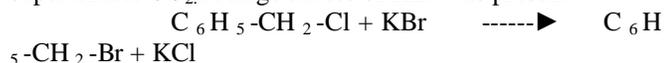
The exceptionally uniform molecular size of the various generations of PAMAM dendrimers makes them excellent size standards for calibration of analytical instruments.

Extraction and Phase Transfer Catalysis in Supercritical Carbon Dioxide

The liquid-like densities and gas-like diffusivities and viscosities of supercritical fluids make them especially attractive for phase transfer catalysis and extraction. Especially CO₂ is interesting because it has a relatively low critical temperature and pressure (31.1 °C and 73.8 bars). Poly (propylene imine) dendrimers, modified with apolar end groups, have been tested for their use as reactive extractant and phase transfer catalyst. In fact a dendritic reactive extractant and phase transfer catalyst can be seen as a unimolecular (polymerized) version of the traditional low molecular weight surfactant or a multi-site version of a traditional tertiary amine phase transfer catalyst.

The dye methyl orange has been extracted using a 5th generation dendrimer (Gf5) into a CO₂ phase and using Gp5 into a tetrachlorocarbon phase. There is almost no solvent effect for the extraction of methyl orange into the core of both Gf5 and Gp5.

The following Sn-2 reversible reaction was performed in supercritical CO₂. A large excess of KBr was present.



Depending on the generation of the dendrimer, the

perfluorooctanyl functionalized dendrimers can catalyze this reaction quite well. The higher the generation, the more the interior of the dendrimer (where the substrate Br- is located) is shielded from the bulk CO₂ phase (where the substrate benzyl chloride is located). This leads to a lower efficiency for the 4th generation dendrimer, as compared to the 2nd and 3rd generation.

Multivalent Bioconjugates

The presence of multiple biologically active molecules on a dendritic scaffold may lead to enhanced effects. These complexes are made by non covalent fictionalization of dendrimer periphery.

Light Harvesting

Light harvesting is the trapping of energy via peripheral chromophores and funneling to a central point where it is converted back into visible light. The dendrimer possesses the properties that facilitate such a conversion. These properties include its tree-like structure that acts as an energy gradient for the funneling of energy. The large amount of absorbing units on the periphery, gives the high probability of capture of light. The relatively short distance from the periphery to the core allows for high efficiency energy transfer. The mechanism begins with the periphery chromophore molecules capturing the energy of photons from light. These photons excite the electrons in the molecules and raise them from their ground state to their excited state. Interchromophore energy transfer then occurs in one of two ways, Dexter excitation transfer, or Forster excitation transfer. In Dexter excitation transfer the energy is transferred through-bond electron exchange. This electron exchange requires a strong donor to acceptor orbital overlap and is therefore a short-range interaction (<10 Å). In Forster excitation transfer the energy is transferred through-space dipole-dipole interaction. In this case, the donor to acceptor orbital overlap is not necessary, allowing the chromophores to be separated by larger distances (10-100 Å). Depending on the monomers used to synthesize the dendrimer that will affect the energy transfer mechanism utilized. Using any of the above energy transfer mechanisms, the energy is channeled to the core where it is converted into visible light.

Catalysis

The dendritic molecule has emerged as an attractive material in the field of catalysis and various dendrimer catalysts have been applied not only to catalytic reactions but also to non-catalytic ones such as nanoscale reactor systems. In the field of catalysis, the hope is that dendrimer catalysts will retain the benefits of homogeneous catalysts (high activity, high selectivity, good reproducibility, accessibility of the metal site and so on), and unlike most other

polymeric species they will be readily recoverable after reaction. In principle, dendrimer is one of the most promising candidates which can meet the needs for an ideal catalyst: persistent and controllable nanoscale dimensions, chemically reactive surface, favorable configurations in which all the active sites would always be exposed towards the reaction mixture so that they are easily accessible to migrating reactants, and soluble but can be easily recovered by filtration. These properties, or some combination of them, are what makes dendrimers so useful not only in catalytic applications but also in non-catalytic ones such as nanoscale reactor systems. In particular, chiral dendrimers have drawn much attention because the highly ordered structures of dendrimers are considered to be suitable for realizing approximately the same chiral environments. Dendrimers make themselves attractive in the design of asymmetric catalysts by combining chirality or asymmetry with their highly symmetrical nature. There are three types of chiral dendrimers according to chiral active sites: 1. Focal point-functionalized chiral dendrimers; 2. Periphery-functionalized chiral dendrimers; and 3. Core-functionalized chiral dendrimers.

Artificial Enzymes

Dendrimers are regular tree-like macromolecules accessible by chemical synthesis from a variety of building blocks. Their topology enforces a globular shape that offers a unique opportunity to design artificial enzymes. Catalytic groups such as metal complexes and cofactors can be placed at the dendrimer core to exploit microenvironment and selectivity effects of the dendritic shell.

Nanocomposites

According to the general concept of reactive encapsulation, dendrimer nanocomposites are made by preorganizing small precursors by an appropriately selected dendrimer. This pre-organization is followed by *in-situ* chemical reaction(s) or physical treatment (irradiation, etc.) that generates reaction products immobilized in a polymeric network. This procedure yields dispersed small domains of guest molecules that are integrated with the dendrimer molecule(s) without creating covalent bonds between the dendrimer and the topologically entrapped matter. It was only recently discovered that PAMAM dendrimers form stable interior molecular nanocomposites with metal cations, zero-valent metals, other electrophilic ligands, and semiconductor particles. These materials are actively being investigated in electronics, optoelectronics and catalysis.

Organosilane Coatings

PAMAM dendrimers are the basis of poly (amidoamine) - organosilane (PAMAMOS) coating technology. PAMAMOS coatings are tough, transparent, flexible coatings, which have many of the same attributes of

PAMAM dendrimers in coating form. They are being investigated for applications in microelectronics.

Inkjet Inks and Toners

PAMAM dendrimers, at low additive levels, dramatically improve water resistance and adhesion of inks to a variety of porous or nonporous substrates such as paper, glass, plastic, or metal. Their water and alcohol solubility permit formulation of low viscous inks. These polymers exhibit Newtonian flow behavior for shear stability in these formulations. In toners, they impart good admix and flow characteristics, stable properties, and high image quality [1].

OTHER APPLICATIONS

There are also some other applications like: for cellular transport, as artificial cells, for diagnostics and analysis, as protein / enzyme mimics or modeling, for manufacture of artificial bones, for development of topical microbicide creams; antimicrobial, antiviral (e.g. for use against HIV) and antiparasitic agents, for biomedical coatings (e.g. for artificial joints), as artificial antibodies and biomolecular binding agents, for carbon fibre coatings and ultra thin films, as polymer and plastics additives (e.g. for lowering viscosity, increasing stiffness, incorporating dyes, compatibilisers, etc.) for creation of foams (i.e. synthetic zeolites or insulating material), as building blocks for nanostructured materials, as dyes and paints, as industrial adhesives, for manufacture of nanoscale batteries and lubricants, as decontamination agents (trapping metal ions), for ultrafiltration, molecular electronics for data storage, 3D optical materials, for light-harvesting systems, quantum dots, liquid crystals, printed wire boards, etc.

Dendrimer Disassembly

Dendrimer disassembly is entirely a new concept in nanotechnology. Dendrimer disassembly is a process that relies on a single triggering event to initiate multiple cleavages throughout a dendritic structure that result in release of individual dendrimer subunits or larger dendrimer fragments. The potential of this process lies in the nature of dendrimers as covalent assemblages of active species, and using the chemistry of disassembly to release these species into a system; and the role of dendritic components of a system in influencing solubility, energy harvesting, or insulating capabilities, and using the chemistry of disassembly to reverse those contributions to a system. This is a powerful construct, in that dendrimers and dendritic structures can be made up of a wide variety of subunits, compatibilized with many different environments, and incorporated into countless systems. Dendritic materials with disassembly capabilities will be useful for traditional polymer degradation technologies and have potential applications in nanotechnology, biomedicine, and sensors.

Biodegradable Dendrimers

The chemical and physical properties of a dendrimer can be optimized by systematically changing the monomer(s). By optimizing the monomer(s), dendrimers can be made to degrade into biodendrimers, which degrade to biocompatible building blocks *in vivo*. Suitable monomers for biodendrimers include α -hydroxy acids, sugars, amino acids, fatty acids, polyethylene glycol, poly caproic acid, and poly (trimethylene carbonate). Factors affecting the degradation rate include: the strength of the chemical bond between the monomers, the hydrophobicity of the dendrimer, the generation and molecular weight of the dendrimer, and the chemical reactivity of the macromolecule. By combining the ideas of drug carriers and degradability, research has recently focused on controlled degradation of dendrimers and release of compounds. Some of the methods to initiate the release include light, removal of protecting groups, and antibodies.

Dendrimer Biocompatibility and Toxicity

The field of biomedical dendrimers is still in its infancy, but the explosion of interest in dendrimers and deodorized polymers as inherently active therapeutic agents, as vectors for targeted delivery of drugs, peptides and oligonucleotides, and as permeability enhancers able to promote oral and transdermal drug delivery makes it timely to review current knowledge regarding the toxicology of these dendrimer chemistries (currently under development for biomedical applications). Clinical experience with polymeric excipients, plasma expanders, and most recently the development of more ‘classical polymer’-derived therapeutics can be used to guide development of “safe” dendritic polymers. Moreover, in future it will only ever be possible to designate a dendrimer as “safe” when related to a specific application. The so far limited clinical experience using dendrimers make it impossible to designate any particular chemistry intrinsically “safe” or “toxic”.

Although there is widespread concern as to the safety of nano-sized particles, preclinical and clinical experience gained during the development of polymeric excipients, biomedical polymers and polymer therapeutics shows that judicious development of dendrimer chemistry for each specific application will ensure development of safe and important materials for biomedical and pharmaceutical use.

Dendrimers as imaging agents

Macromolecular contrast agents have become very important tools of modern diagnostic medicine. An early application of dendrimer to imaging technology was disclosed in the US patent. The patent discloses the new stable complexing agent for radionucleotide-derivatized phosphonated dendrimers imaging the skeletal system in mammals. Dendrimers provide multiple binding sites on the periphery, allowing many magnetic resonance imaging (MRI) contrasting agent complexes to attach to them. One dendrimer molecule can host up to 24 contrasting agent complexes (depending on generation), thereby attaining a higher signal to noise ratio.

Dendritic Catalysts / Enzymes

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra filtration methods. Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Because of their ‘pseudo’-spherical nature and their resultant conformations the metal sites in these well defined polymeric catalysts should be easily accessible for substrate molecules and reagents, and therefore exhibit characteristics- fast kinetics, specificity and solubility [1,7].

Table 1: Comparison of Properties of Dendrimer and linear polymers ^[4,5.]

Sr. No.	Property	Dendrimers	Linear Polymers
1	Structure	Compact, Globular	Not compact
2	Synthesis	Careful & stepwise growth	Single step polycondensation
3	Structural control	Very high	Low
4	Architecture	Regular	Irregular
5	Shape	Spherical	Random coil
6	Crystallinity	Non-crystalline, amorphous materials -lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7	Aqueous solubility	High	Low
8	Nonpolar solubility	High	Low
9	Viscosity	Non linear relationship with molecular weight	Linear relation with molecular weight
10	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydispense

Figure 1: Structure of a Dendrimer

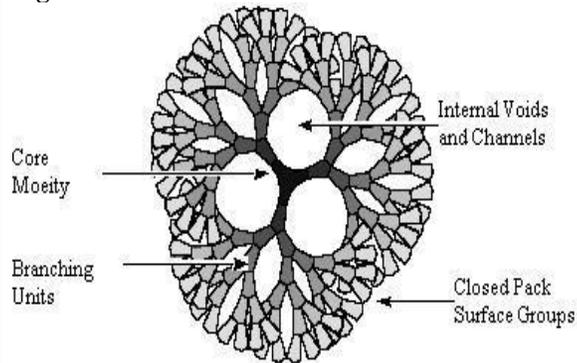


Figure 3: Divergent growth method

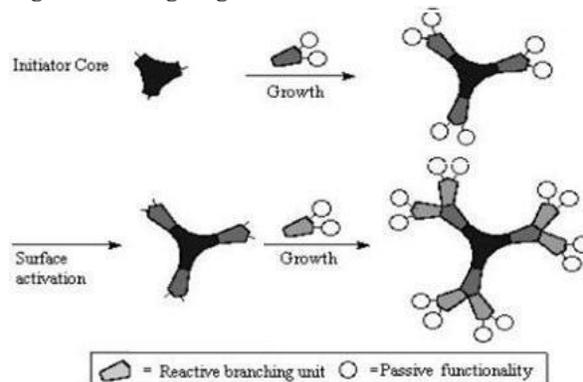


Figure 2: Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface

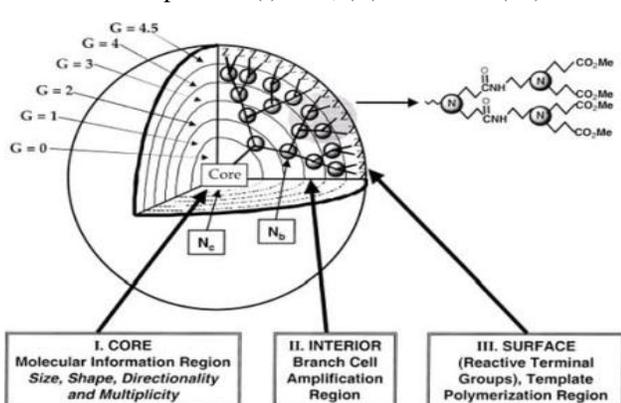


Figure 4: Convergent growth method

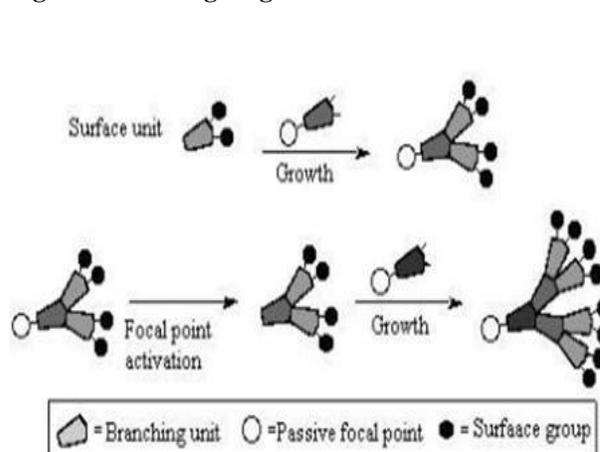


Fig. 5: Double Exponential and Mixed Growth

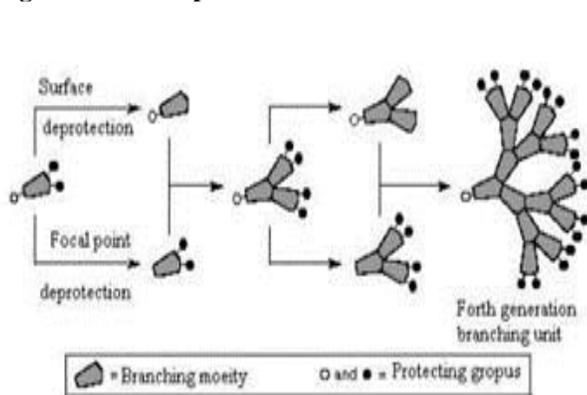


Figure 6: Three-dimensional structure of a G6-PAMAM dendrimer, under different pH.

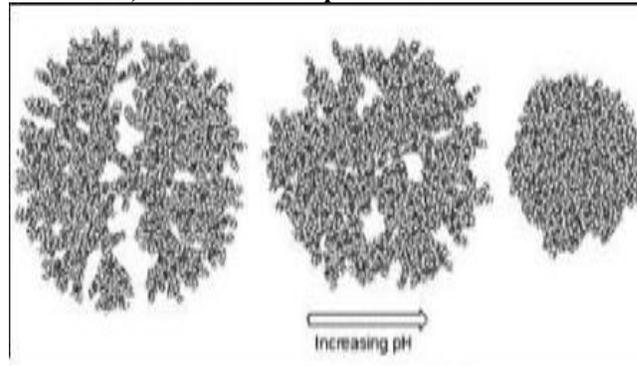


Figure 7: Two-dimensional depiction of conformational changes upon different pH of a carboxy-terminated PPI-dendrimer.

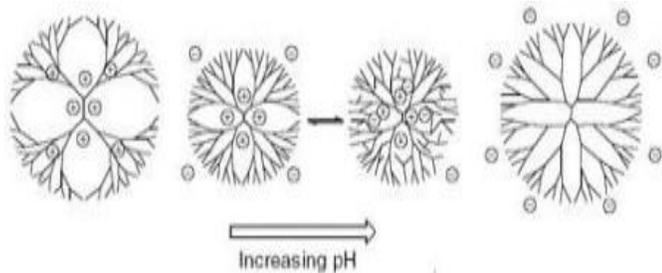


Figure 10: Dendrimer at different concentrations (a) Dilute (b) Contact (c) Collapse (d) Interpenetrate

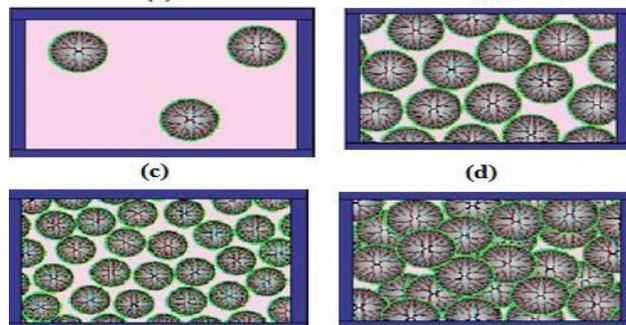


Figure 8: Proposed scheme for solvation of a dendrimer under different solvent conditions. (a) Solvation of a polar dendrimer in a protic solvent (“good”) leading to extended conformation exposing a polar surface. (b) Solvation of a polar dendrimer in an apolar aprotic solvent (“poor”) leading to exposure of an apolar surface consisting of alkyl chains by back-folding.

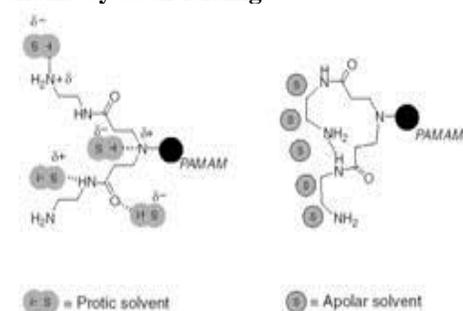


Figure 11: Applications of Dendrimers

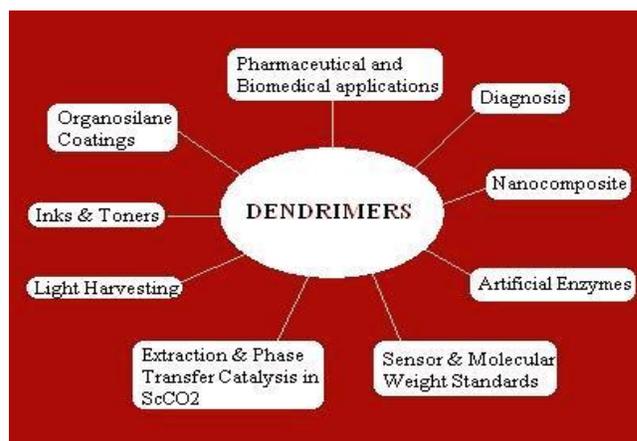


Figure 9: The three-dimensional conformational change of a PPI dendrimer upon increasing ionic strength

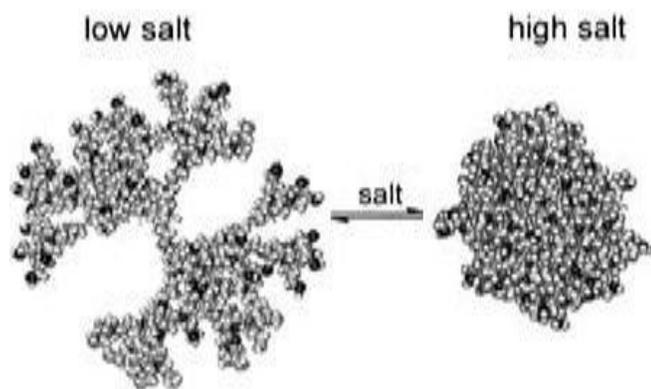


Figure 12: The encapsulation of anticancer drugs methotrexate (left) and 5-fluorouracil (right) into PEGylated generation 3 and 4 PAMAM dendrimers.

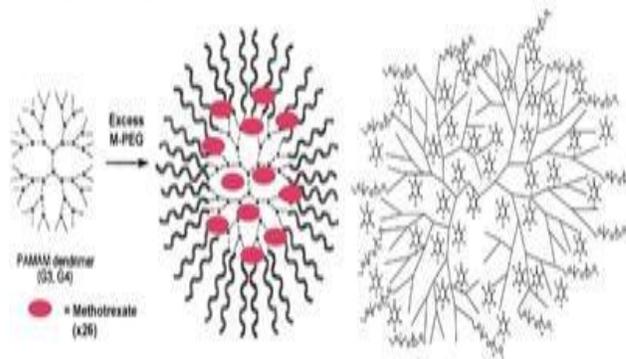
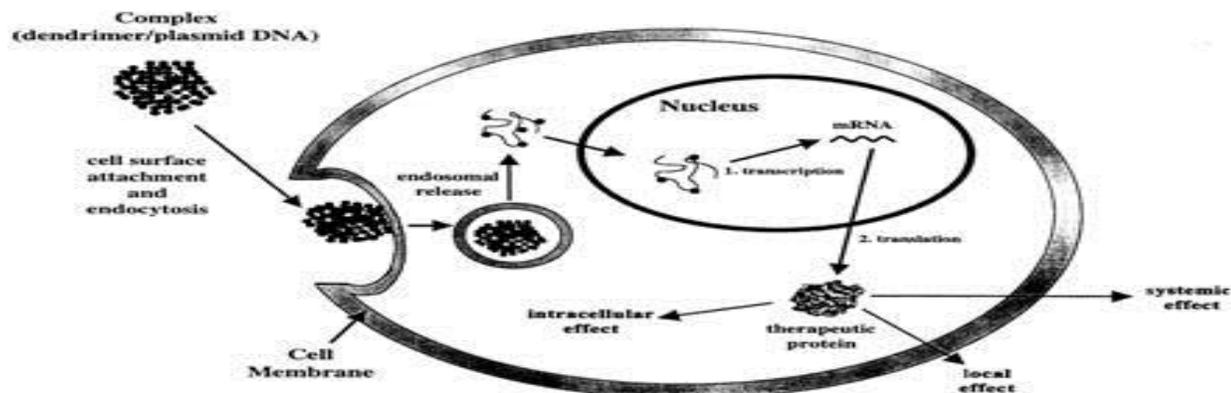


Figure 13: Dendrimer involved in gene Transfection



CONCLUSION

The dendrimers holds in a promising future in various pharmaceutical applications and diagnostic field in the coming years as they possess unique properties, such as high degree of branching, multi valency, globular architecture and well defined molecular weight, there by offering new scaffolds for drug delivery. Dendrimers are expected to play a key role in biomedical fields in the 21st century. They provide platforms for drug attachment and have the ability to encapsulate or bind drugs via several mechanisms. An increasingly large number of drugs being developed today facing problems of poor solubility, bioavailability and permeability. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs. Also the problem of biocompatibility and toxicity can

be overcome by careful surface engineering. Recent successes in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also as research progresses, newer applications of dendrimers will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

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