International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.4, No.1, pp 432-451, Jan-Mar 2012

Dendrimer: Globular Nanostructured Materials for Drug Delivery

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Abstract: Nanotechnology is an emerging research field that helps in reviving the structural design, synthesis and fabrication at the molecular magnitude. There are approximately 130 nanopharmaceutical products in development including~nanoparticles, nanocrystals, dendrimers, liposomes and micelles. The increase in the selectivity and stability of therapeutic agents can be achieved with the help of Nanoparticle drug-delivery system. But due to several factors such as drug leakage, reticuloendothelial system, (RES) uptake, immunogenicity, hydrophobicity, hemolytic toxicity, cytotoxicity, the use of nanostructures are restricted. These challenges can be overcome by surface engineering the dendrimer with bioactive agents either encapsulating into the interior of the dendrimer or by physically adsorbing them onto the surface of the demdrimer. Thus this surface engineering help to achieve the desired properties of the carrier as per the requirement of the active ingredient and it also gives an access for new potentially relevant polymer architectecture Some of the examples for surface engineering of dendrimers are Polyester dendrimer, Arginine dendrimer, Glycodendrimers, Citric acid dendrimer ,PEGylated dendrimers, etc.
Key words: Dendrimers, nanostructured drug carriers, drug delivery.

INTRODUCTION

Dendrimers are repeatedly branched macromolecules or nano-sized, radially symmetric molecules with well-defined, homogeneous and monodisperse structure consisting of tree-like arms or branches. The name comes from the~Greek~word Dendron which translates to tree. Dendrimers are globular or spheroid nanostructures that are engineered to encapsulate the molecules into their interior void spaces or to attach onto the surface [1]. Shape, size, and reactivity are determined by interior branching, surface functionalities, generation (shells) and chemical composition of the core. Dendrimers are constructed through a set of repeating chemical synthesis procedures that build up from the molecular level to the nanoscale region under conditions that are easily performed in a standard organic chemistry laboratory. The dendrimer diameter increases linearly where as the number of surface groups increases geometrically. Dendrimers are very uniform with extremely low polydispersities, and are generally created with dimensions incrementally grown in approximate nanometer steps from 1 to over 10nm. The control over size, shape and surface functionality makes dendrimers one of the commercially available smartest nanotechnologies [2]. Divergent synthesis was the first introduced method for the production of dendrimers by Vogtle in 1978, Denkewalter at~Allied Corporation~as in 1981 Donald Tomalia at Dow Chemical in 1983 [3] and 1985[4] and by Newkome [5,6] in 1985. In 1990 a convergent synthetic approach was newly introduced by Jean Frechet after which dendrimer popularity

increased to a rate of more than 5,000 scientific papers and patents by the year 2005.

CLASSIFICATION OF DENDRIMERS:

The following classification for the commonly reported dendrimer types although few dendrimer types may fit in one or more types of classes.

a. Simple dendrimers
b. Liquid crystalline dendrimers
c. Chiral dendrimers
d. Micellar dendrimers
e. Hybride dendrimers
f. Amphiphilic dendrimers
g. Metallodendrimerrs

STRUCTURE

Dendrimer formation is initialised from an atom such as nitrogen onto which carbon and other elements are attached by repeating series of chemical reactions to produce a spherical branching structure. The resulting dendrimers will have a size similar to albumin and hemoglobin, but smaller size than multimers such as the IgM antibody complex.

Dendrimers possess three distinguished components[8],[9] namely,

An initiator multi-functional core

(i) Interior layers (generations) with repeated branching units, which are radically attached to the core

(ii) Exterior surface functional group (terminal functionality) attached to the outermost interior layers.

Figure 1: General structure of Dendrimer and Dendron.

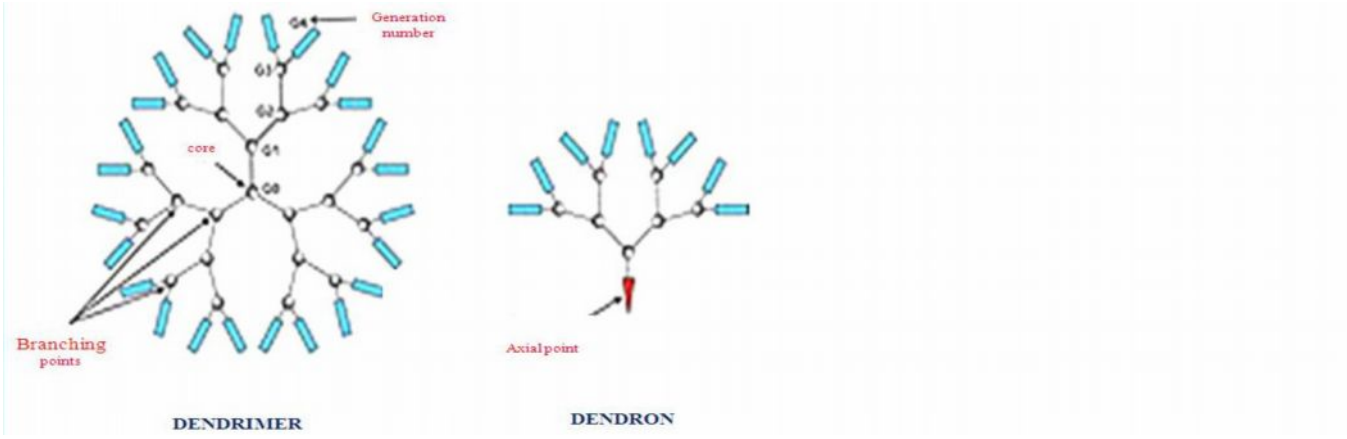
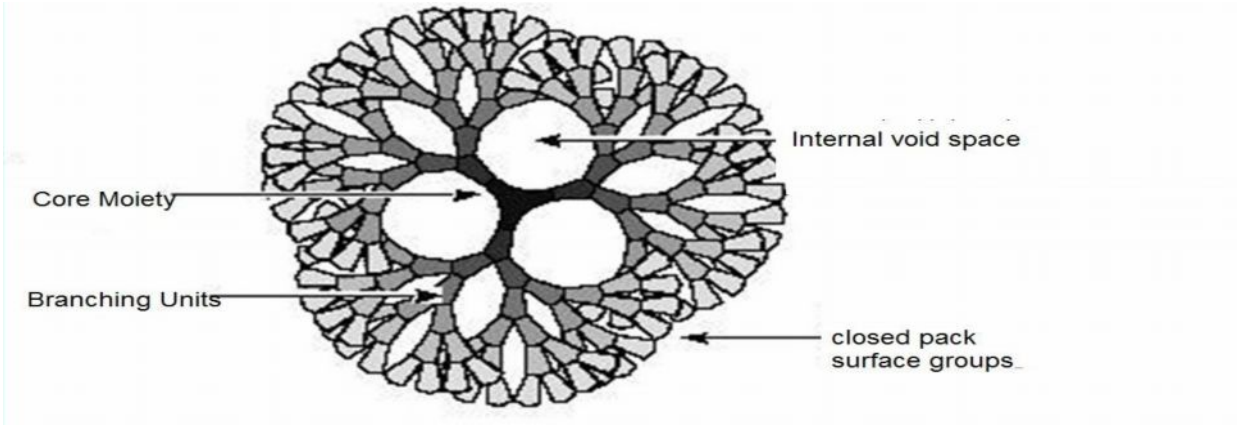


Figure 2: The Dendritic Structure



COMPONENTS OF A DENDRIMER STRUCTURE

PINCER

The outer shell of dendrimers contains a varying number of pincers formed by the last focal point headed before the dendrimer surface. Due to the division in the chain of dendrimers at the focal points, the number of pincers in the PPI and PAMAM dendrimers becomes half the number of the surface groups present.

SHELL

The dendrimer shell is the generation space (i.e the homo-structural spatial segment) between the focal points. The space between the last outer branching point and the surfaceis the outer shell and the inner shells are generally known as the dendrimer interior.

GENERATION

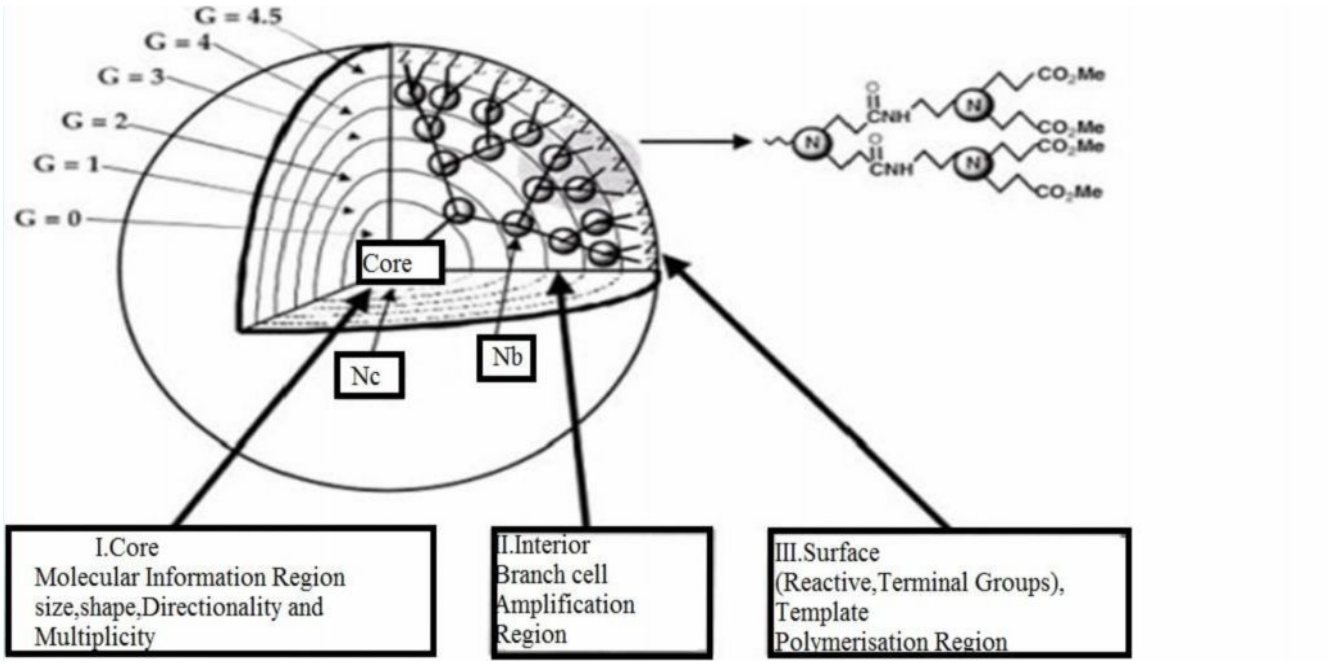
It is the hyperbranching when going from the centre of the dendrimer towards the periphery, resulting in homostructural layers between the focal points (branching points). Generation number is the number of focal points present in the dendrimer counting from the core towards the dendrimer surface i.e a dendrimer having five focal points when moving from the centre towards the periphery is signified as the 5th generation dendrimer and abbreviated as G5-dendrimer.

E.g: A 5th generation polypropylene imine is abbreviated to a G5-PPI dendrimers. The core of the dendrimer is sometimes designated as generation zero (G0) i.e the core structure have no focal points, as hydrogen substituents are not considered as focal points. Intermediates formed during the dendrimer synthesis are sometimes termed as half-generations; for example the PAMAM dendrimers terminated with carboxylic acid.

END-GROUP

End groups are generally referred as the the surface group of the dendrimer or terminal group. Dendrimers terminated with amine end-groups are named as amino-terminated dendrimers.

Figure 3: Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior and (III) surface



TYPES OF DENDRIMERS

Types	Definition	Synthesis	Example	Applications
Pamam Dendrimer	Poly (amidoamine) dendrimers possess amino groups on the surface.	Divergent	Dendritech™ (USA)	Material Science and Biomedicine Computer toners
Pamamos Dendrimer	Inverted unimolecular micelles consists of hydrophilic nuclephilic PAMAM interiors and hydrophobic organosilicon(OS) exteriors.	Convergent and Divergent	SARSOX	Nano-lithography Electronics Photonics Chemical catalysis Precursor for honey-comb like network preparations.
PPI dendrimer	Poly-alkyl amines having primary amines as end groups and its interior consists of numerous tertiary tris-propylene amines.	Divergent	Asramol by DSM (Netherlands)	Material science and biology
Tecto dendrimer	Composed of a core dendrimer with multiple dendrimers at its periphery	Divergent	Stratus® CS Acute Care TM, Starburst®,Mercapto	Diseased cell recognition Diseased state drug delivery diagnosis Reporting location to outcome of therapy
Chiral dendrimers	Chilarity is based on construction of constitutionally different but chemically similar branches to a chiral core.	convergent	chiral dendrimers derived from pentaerythritol.	Biomedical applications, chiral catalyst
Hybrid dendrimers	Combination of dendritic and linear polymer in hybrid block or graft copolymer forms	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes	Biomedicals, Molecular electronics, Nanophotonics,Sensing.
Amphiphilic dendrimers	Unsymmetical globular dendrimers built with two segregated sites of chain end.	Divergent	SuperFect, Hydra-amphiphiles and bola-amphiphiles	Structure-directing agent, Use as polar part, cell and gene transfection.
Micellar dendrimers	Unimolecular micelle structure of Water soluble hyperbranched polyphenylene	Divergent	Beclomethazone dipropionate, NX-200, Magnevist®	Biological and medical applications,Drug delivery, Imaging agent.
Multiple antigen peptide dendrimers	Dendron-like molecular construct based upon a polylysine skeleton.	Convergentsynthesis	VivaGel	Used in vaccines and diagnostic research. Biological applications.

Frechet-type dendrimers	Dendrimes having carboxylic acid groups as surface groups and containing poly-benzyl ether hyperbranced skeleton.	Convergentsynthesis	Frechet type dendron azides, Priostar™	Drug carrier, Purifiers, Organic synthesis, detecting agent, drug delivery.
Liquid crystalline dendrimers	Consists of mesogenic monomers	divergent	Polycanter liquid crystals, Mesogen functionalized carbosilane dendrimers	Science and Engineering.
Metallo dendrimers	Dendrimers with incorporated metal atoms	Convergent	Zinc Porphyrin dendrimers(M=Zn)	Sensing Catalytic applications, mimic biomolecules, light-harvesting, Biomarkers.
Peptide dendrimers	Dendrimers having peptides on the surface and incorporating amino acids as branching or core units.	Convergentsynthesis	, Beta-Casomorphin(human)	Drug delivery contrast agents for MRI, MRA , fluorogenic imaging and sero diagnosis, protein mimetic.

SYNTHESIS

Three major portions in dendrimers are: a core, an inner shell and an outer shell. Ideally, a dendrimer with different functionality in each of these components can be synthesized to control properties such as thermal stability, solubility and attachment of compounds for certain applications. Synthetic processes can also precisely control the size and number of branches on the dendrimer. Dendrimers are perfect artificial macromolecules, which are synthesized by a stepwise method such as divergent and convergent synthesis.

The synthesis reactions include many steps required to protect the active site and it is complicated to synthesize dendrimers in all the methods. Thus dendrimers are hard to make and very expensive. At present, only few companies commercialise dendrimers; eg Polymer Factory [12] commercializes biocompatible bis-MPA dendrimers and Dendritech[13] is the producers of PAMAM dendrimers. Figure 4: Schematic of divergent and convergent method synthesis of dendrimers.

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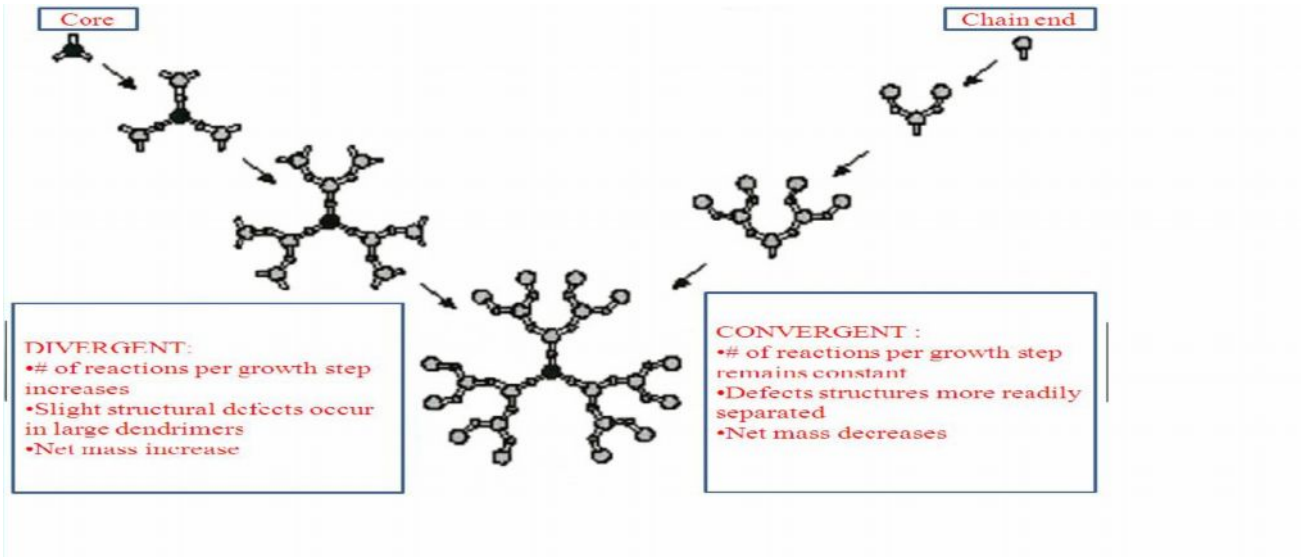


1. DIVERGENT METHODS

This method starts from a central core and extends towards the surface by a series of reactions, commonly a Michael reaction [14]. Dendrimers are polymers that radiate out from a central core, with the number of branch points on a given arm increasing exponentially from the core to the periphery. Every step of the reaction should reach an absolute completeness to prevent errors in the dendrimer, which might cause trailing generations (branches with unequal length). Such impurities can affect the functionality and symmetry of the dendrimer, but due to the relative small size difference between perfect and imperfect dendrimers , they are extremely difficult to purify out .The divergent approach is a successful method for the production of large quantities of dendrimers.

2. CONVERGENT METHODS

Construction of dendrimer in thismethod is an stepwise process which begins from the end groups and progresses inwards[15. When the growing branched polymeric arms, called dendrons, are large enough, they are attached to a multifunctional core molecule. This method prevents the formation of high shells due to the chance of steric problems that might take place in the reactions of the dendrons and the core molecule. This is a relatively easy approach to eliminate impurities and to form shorter branches along the way, finally to form a monodispersed dendrimer.

GENERAL PROPERTIES OF DENDRIMERS:

Dendritic molecules are characterized by structural perfection. Dendrimers and dendrons are monodisperse, usually highly symmetric and spherical compounds. The field of dendritic molecules can be divided into high-molecular weight and low-molecular weight species. The former includes hyperbranched polymers, dendronized polymers and the polymer brush while the latter includes dendrons , dendrimers etc.

The multiple interactions between surface amines and nucleic acid phosphates are also significant for the formation of dendrimers and DNA complexes. Solubility of the dendrimers depends on the nature of surface groups. Dendrimers with hydrophilic groups at ends are soluble in polar solvents, while dendrimers that terminate with hydrophobic groups are soluble in nonpolar solvents. In a solubility test with tetrahydrofuran (THF) as the solvent, the solubility of dendritic polyester was found remarkably higher than that of analogous linear polyester and a significant chemical reactivity also observed.

Table 1: Properties Of Dendrimer And Linear Polymers [16],[17],[18],[19],[20]

Serial Number	Property	Dendrimers	Linear Polymers
1	Structure	Compact and Globular	Not compact
2	Shape	Spherical	Random coil
3	Architecture	Regular	Irregular
4	Structural control	Very high	Low
5	Synthesis	Stepwise growth	Single step polycondensation
6	Crystallanity	Non-crystalline and amorphous materials Lower glass temperatures	Semi crystalline/crystalline materials -Higher glass temperatures
7	Reactivity	High	Low
8	Aqueous solubility	High	Low
9	Nonpolar solubility	High	Low
10	Viscosity	Non linear relationship with molecular weight	Linear relation with molecular weight
11	Ionic conductivity	High	Low
12	Compressibility	Low	High
13	Polydispersity	Monodi sperse	Polydisperse

VARIOUS FACTORS AFFECTING THE PROPERTIES OF DENDRIMERS

1. EFFECT OF PH ON DENDRIMERS[22]

At high pH the dendrimer is uncharged and the formation of any DNA-dendrimer complex is not seen. At neutral pH, when the dendrimer is positively charged due to the protonation of all the primary amines, the strong electrostatics interaction helps the DNA strand collapse onto the dendrimer. Amino-terminated PPI and PAMAM dendrimers have basic surface groups as well as a basic interior. PPI and PAMAM dendrimers that contains tertiary amines, the region with low pH extends the conformations because of the electrostatic repulsion between the positively charged ammonium groups. Molecular dynamics can be applied to find the structural behaviour of PAMAM dendrimers as a function of pH which show that the dendrimer has an extended conformation, based on a highly ordered structure at low pH (pH<4). At this pH, the interior becomes hollow with the increase in the generation number due to the repulsion between the positively charged amines both at the tertiary amines in the interior and surface of the dendrimer. At neutral pH, back-folding occurs due to the hydrogen bonding between the positively charged amines at the surface and the uncharged tertiary amines in the interior. At higher pH (pH>10) the dendrimer contracts as the charge of the molecule gets neutralised, attaining a more spherical (globular) structure, where the repulsive forces between the surface groups and the dendrimer arms reaches a minimum.[23] At this pH, the conformation has a higher degree of back-folding as a result of the weak inter-dendron repulsive forces.[24],[25] The pH-dependent conformational changes of PPI dendrimers having acidic (carboxylic acid) end-groups is different as compared to amino-terminated counterparts. Measurement of self diffusion using Small angle neutron scattering (SANS) and NMR at different pH values show that the dendrimer core has the most extended conformation at pH 2 due to the electrostatic repulsion between the positively charged protonated tertiary amines, leading to a large radius of the core, whereas at pH 6 the dendrimer reaches its minimum radius, where the amount of positively charged amines equals the amount of negatively charged carboxylic groups (isoelectric point) forming a dense core conformation which is more subjective to back-folding [26]. Thus, at pH 6 due to the attractive interactions between the negatively charged surface carboxy-groups and the positively charged tertiary amines in the inner shells of the dendrimer , some degree of back-folding [26]. 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.

2. EFFECT OF SOLVENT ON DENDRIMERS

Conformational state of the dendrimer can be investigated according to the solvent ability to solvate the dendrimer structure. With the decrease in solvation dendrimers of all generations generally experience a larger extent of back-folding. The highest tendency towards back-folding is shown by the low generation dendrimers due to poor solvation compared to the higher generation dendrimers. NMR studies performed on PPI dendrimers reveals that a nonpolar solvent like benzene, poorly solvates the dendrons favouring intramolecular interactions between the dendrimer segments and back-folding. In turn, 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[27].

Figure 5: Two dimensional depiction of conformational changes upon different pH of a carboxy-terminated PPI-dendrimer

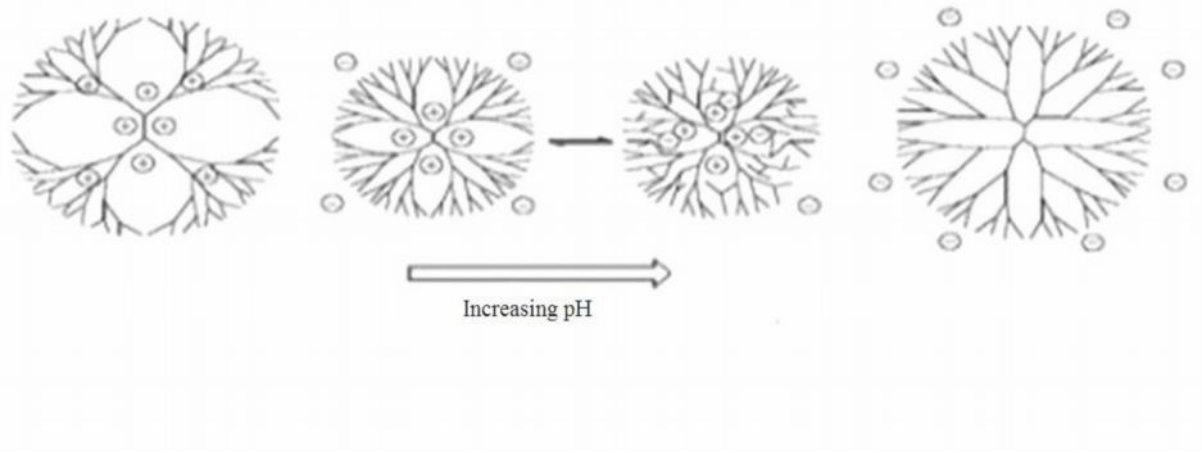
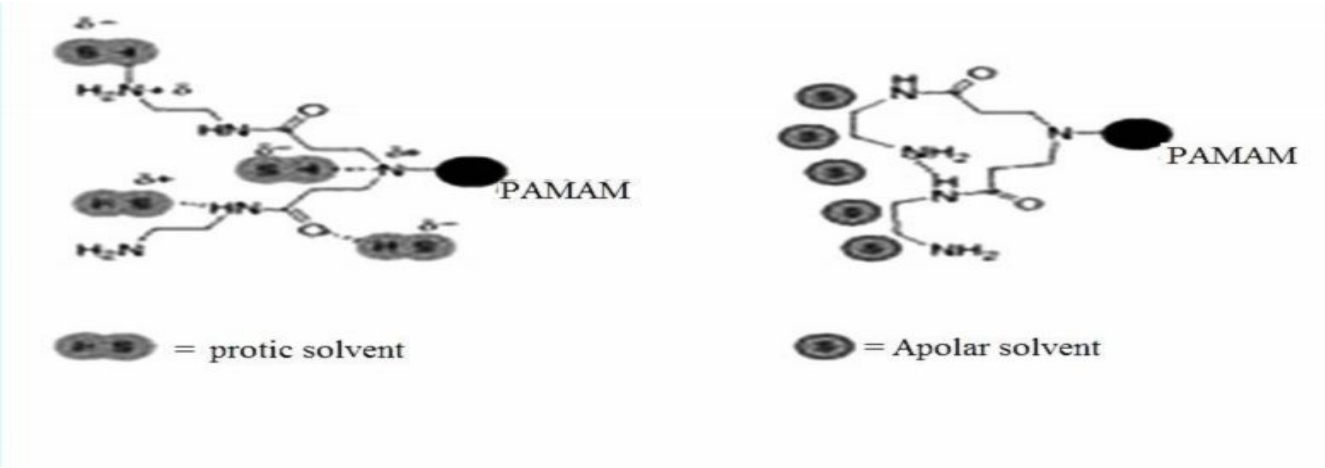


Figure 6: Two dimensional depiction of conformational changes upon different pH of a carboxy-terminated PPI-dendrimer



Both experimental as well as theoretical studies on amino-terminated PPI and PAMAM dendrimers (polar dendrimers) show that a higher molecular density is induced when polar (good) solvents solvate the dendrimer arms whereas higher molecular densities in the core regionis induced by nonpolar aprotic (poor) solvents as a result of back-folding [28].Decrease in the surface polarity of back folded dendrimer can be achieved by the back-folding of the polar surface groups which may expose the more hydrophobic dendrimer parts to the surroundings [29],[30]. Figure 6: 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.

3. EFFECT OF SALT ON DENDRIMERS

Salts with 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[31],[32]. At low salt conditions, in order to minimize charge repulsion in the structure the repulsive forces between the charged dendrimer segments forms an extended conformation.

4. EFFECT OF CONCENTRATION OF SOLVENTS, SALTS

In dendrimers with flexible structures the conformation is affected by small molecules like solvents, salts or protons and larger objects, such as other dendrimers or surfaces which can have a great affect on the molecular conformation and density of the dendrimer. Small angle X-ray scattering (SAXS) experiments performed on PPI dendrimers (G4, G5) witih a polar solvent like methanol show that the molecular conformation of dendrimers contracts with increase in the concentration. This molecular contraction may minimize the repulsive forces between the dendrimer molecules and also the ability of the dendrimers to exhibit a more tight intermolecular packing can be increased [33].

METHODS FOR CHARACTERIZATION OF DENDRITIC POLYMER

The methods that can be used for characterization of dendritic polymers are:[34]

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

   Nuclear Magnetic Resonance (NMR): Nuclear Magnetic Resonance is widely used in characterizing dendrimers. NMR analysis are done routinely during the step by step synthesis of dendrimers till higher generations as it gives information about the chemical transformations undergone by the end groups.

   Infra-red (IR) and Raman: Infra-red spectroscopy is mainly used for the routine analysis of the chemical transformations occurring at the surface of dendrimers, such as the disappearance of nitrile groups in the synthesis of PPI dendrimers, the occurrence of hydrogen bonding in PPI glycine functionalized dendrimers, or the disappearance of the aldehydes during the synthesis of PMMH dendrimers.

Ultra-violet-visible (UV-VIS): UV-Visible spectroscopy can be used to monitor the synthesis of dendrimers. UV-Visible spectrometry for its simplicity, versatility, speed, accuracy and cost-effectiveness.

Fluorescence: In fluorescence spectroscopy, the species is first excited, by absorbing a~photon, from its ground electronic state to one of the various vibrational states in the excited electronic state. When collided with other molecules, this collision causes the excited molecule to lose vibrational energy and reach the lowest vibrational state of the excited electronic state.

The molecule then drops down to one of the various vibrational levels of the ground electronic state again, emitting a photon in the process. Thus,the emitted photons will have different energies and frequencies. Fluorescent spectroscopy used to analyse the different frequencies of emitted light along with their relative intensities, the structure of the different vibrational levels can be determined.

Chirality: Chiral amino acids linked to the surface of PPI dendrimers induce a dramatic decrease of optical rotation on going from G1 to G5 [35], rigid paracyclophanes on the surface of PPI dendrimers have a nearly constant optical activity with increasing generation [36], whereas chiral benzylamine[37] or ferrocene [38] linked to the surface of PMMH dendrimers give simply additive optical rotation values. When a single chiral group such as aminophenylpropanediol [39] or binaphthyl [40] is located at the core of PBzE dendrimers, the optical rotation decreases with the increase in generation. In the latter case, the CD data affords information about the variation of the dihedral angle u in the binaphthyl [41]. For fully chiral dendrimers (throughout the structure), the chiroptical properties of two series of chiral polyarylether dendrimers from generation 0 to 3 (up to 45 stereogenic centres) [42] and of dendrimers based on dihydroxypyrrolidine [43] show that the CD spectra change dramatically, indicating conformational substructures in the branches. On the other hand, the CD spectra of a series of fully chiral dendrimers of phenylalanine type up to G2 show little steric interaction, but molar rotation divided by the number of stereogenic centres decreases with increasing size of the dendritic structure [44]. On the contrary, the molar rotation of a series of polyether dendrimers up to G4 is approximately proportional to the number of chiral units [45]. For dendrimers having one layer of chiral ferrocenes located inside the structure, the chiroptical properties are not sensitive to the location of the chiral units inside the dendrimers, up to G11.

Circular dichroism (CD): Circular dichroism (CD) spectroscopy measures the difference in the absorption of left-handed polarized light versus right-handed polarized light which occurs due to structural asymmetry. The absence of regular structure results in zero CD intensity, while an ordered structure results in a spectrum which can contain both positive and negative signals.

X-ray diffraction: This technique should allow precise determination of the chemical composition, size and shape of dendrimers. X-ray diffraction (XRD) is a versatile, non-destructive technique that reveals detailed information about the chemical composition and crystallographic structure of natural and manufactured materials.

Mass spectrometry: Classical mass spectrometry techniques such as chemical ionization or fast atom bombardment (FAB) are used for the characterization of small dendrimers, whose mass is below 3000 D due to their mass limitation [46]. For higher molecular weights, techniques developed for the characterization of proteins and polymers have to be applied. Electro-Spray Ionisation (ESI) can be used for dendrimers able to form stable multicharged species. It has been applied to PPI dendrimers[47], and to PAMAM dendrimers up to generation 10 [48]. The dendrimers were also characterized by mass spectrometry using matrix-assisted laser desorption ionization (MALDI). MALDI-TOF Mass spectrometry was used to obtain the molecular weight information and to determine the purity, existence of dimers, trimers, and trailing generations in the sample.

2. Electrical techniques like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis. Electron paramagnetic resonance (EPR): Stable radicals have been either grafted on the surface of dendrimers or generated inside the structure at the branching points and analysed by EPR. EPR was used for the quantitative determination of the substitution efficiency on the surface of PAMAM dendrimers [49] or was able to detect interactions between the end groups of large PPI dendrimers[50].

   Electrochemistry: Exhaustive coulometry has been used to measure the number of electroactive groups. The degree of burying of electroactive groups inside dendrimers can be detected by cyclic voltammetry. Electrochemistry gives information about the possibility of interaction [51] of electroactive end groups between them, traducing a close proximity.

Electrophoresis: This technique was used for the assessment of purity and homogeneity of several types of water-soluble dendrimers such as PAMAM dendrimers having NH3 + or CO2_ end groups[52] PLy dendrimers [53], PPI dendrimers [54], nucleic acid dendrimers [55], or phenylacetylene dendrimers [56]. Gel electrophoresis was also used for studying the interaction between positively charged dendrimers and DNA.

3. Scattering techniques like Small angle neutron scattering (SANS),Small angle X-ray scattering (SAXS) and Laser light scattering (LLS).
   Small angle X-ray scattering (SAXS): The SAXS technique is often used for the characterization of polymers [57]; applied to dendrimers it gives information about their average radius of gyration (Rg) in solution.The intensity of the scattering as a function of angle also provides information on the arrangement of polymer segments, hence on the segment density distribution within the molecule. This technique was applied to fluorinated carbosilane dendrimers [58] and PAMAM dendrimers [59] to afford their Rg values. The angular dependence of the scattered intensity indicates a relatively diffuse, open boundary for G3 PAMAM, and a very sharp outer boundary for G10, with a gradual transition from star-like (G3) to sphere-like (G10) entities [60].
   Small Angle Neutron Scattering (SANS): The SANS technique also gives access to the radius of gyration, but may also reveal more accurate information than SAXS about the internal structure of the entire dendrimer. In particular, SANS may indicate the molecular weight; such experiments have been conducted with PPI [61], PAMAM [62] and PBzE dendrimers [63]. The location of the end groups has also been determined by SANS experiments conducted with PAMAM dendrimers and PPI dendrimers having labelled (deuterated) or unlabelled end groups; in the former case, the end groups are concentrated near the periphery [64], whereas in the latter cases the end groups are located throughout the structure [65]. A recent extension of this technique (neutron spin-echo) was applied to PAMAM dendrimers[66].This also been applied to aggregates of PBzE dendrimers having a phthalocyanine core, and to vesicles formed by the self-assembly.
   Laser light Scattering (LLS): In most cases, the Laser Light Scattering technique is used as a detector coupled to size exclusion chromatography apparatus (see later), to determine the hydrodynamic radius of dendrimers. However, in some cases, it has been used for the direct analysis of samples of dendrimers in solution; for instance, the molecular weight (Mw) of PPI dendrimers has been evaluated with low-angle LLS [67]. Dynamic LLS is mainly used for the detection of aggregates; it has been applied to aggregates of PBzE dendrimers having a phthalocyanine core [68], and to vesicles formed by the self-assembly of some water soluble PMMH dendrimers [69].
4. Microscopy like Scanning electron microscopy, Transmission electron microscopyand atomic force microscopy
   Transmission electron microscopy: In Transmission Microscopy, electrons or light produce images that amplify the original, with a resolution ultimately limited by the wavelength of the source. Scanning electron microscopy: In scanning microscopy such as Atomic Force Microscopy (AFM), the images are produced by touch contact Q at a few angstroms of a sensitive cantilever arm with the sample.
   Atomic force microscopy: The AFM, however, has the advantage of imaging almost any type of surface, including polymers, ceramics, composites, glass, and biological samples.
5. Size exclusion chromatography(SEC) Size Exclusion (or Gel Permeation) Chromatography allows the separation of molecules according to size. A detector such as a differential refractive index or a LLS detector (see above) is connected to the SEC apparatus for the determination of the polydispersity, which is generally very close to unity. Most types of dendrimers were characterized by SEC, even self-assembled dendrimers.
6. Rheology, physical properties by Dielectric spectroscopy (DS) and Differential Scanning Calorimetry (DSC)
   Differential Scanning Calorimetry (DSC): The DSC technique is generally used to detect the glass transition temperature (Tg), which depends on the molecular weight, entanglement and chain-end composition of polymers. The Tg is affected by the end group substitutions, and the molecular mass for PBzE dendrimers [70], and correlates with ne /M (ne is the number of chain ends) [71]. The same behaviour was observed for phosphorus dendrimers [72], and to a lesser extent for PPI dendrimers [73], whereas the generation has practically no influence on the Tg values of liquid crystal dendrimers based on poly(phenyl acetylene) [74] or carbosilazane dendrimers [75]. DSC and Temperature Modulated Calorimetry (TMC) were also used to detect physical aging of PMMH dendrimers [76].
   Dielectric spectroscopy (DS): Dielectric spectroscopy gives information about molecular dynamic processes in polymers (a-, h-, g-, and y-

relaxation). This technique was applied to various types of dendrimers, and it was generally found that the a-relaxation values obtained by DS agree well with those obtained in Differential Scanning Calorimetry measurements. Carbosilane [77], ARB [78], poly(ether amide) [79] PMMH[80],[81] and carbosilazane dendrimers [82] were analyzed by DS; in most cases, both the a- and hrelaxations were obtained and identified.

7. Miscellaneous: X-ray Photoelectron Spectroscopy (XPS): it s useful for the measurements of dipole moments, titrimetry, and uses soft x-rays (with a photon energy of 200-2000 eV) to examine core-levels .The XPS technique is highly surface specific due to the short range of the photoelectrons that are excited from the solid. The energy of the photoelectrons leaving the sample are determined using a~CHA~and this gives a spectrum with a series of photoelectron peaks. The binding energy of the peaks are characteristic of each element. The peak areas can be used (with appropriate sensitivity factors) to determine the composition of the materials surface. The shape of each peak and the binding energy can be slightly altered by the chemical state of the emitting atom. Hence XPS can provide chemical bonding information as well. XPS is not sensitive to hydrogen or helium, but can detect all other elements.

APPLICATION OF DENDRIMERS:

1. DENDRIMERS DRUG DELIVERY: TARGETED AND CONTROLLED RELEASE DRUG DELIVERY

here are attempts to use dendrimers in the targeted delivery of drugs and other therapeutic agents. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers have drawn attention as drug carriers due to their unique properties mainly their well defined three-dimensional structure, their low polydispersity , the availability of many functional surface groups and their ability to mimic. Dendrimers can act as drug carriers either by interacting with drugs at their terminal functional groups via covalent bonds or electrostatic forces (prodrug) or by the encapsulation of drugs within the dendritic structure. Dendrimers can be used as coating agents to protect or deliver drugs to specific sites in the body or as time-release vehicles for biologically active agents. Therapeutic agents can also be attached to a dendrimer to direct the delivery. A good example of such application is using dendrimers in Boron Neutron Capture Therapy (Bnct).

2. DELIVERY OF ANTICANCER DRUGS BY DENDRIMERS AND DENDRITIC POLYMERS

Cancer is caused by damage of genes which control the growth and division of cells. Cancer can be cured by rectifying the damaging mechanism of the genes or by stopping the blood supply to the cell or by destroying completely using the conventional treatments such as surgery, radiation therapy and chemotherapy. These treatments have their own limitations. Hence certain nanoparticles can be designed to absorb certain wavelength of radiation, which burns the cancer cells.In specific Nanoparticles , a single dendrimer can carry a molecule that recognize cancer cells, a therapeutic agent to kill those cells and a molecule that recognize the signal of cell death. Researchers hope to manipulate dendrimers to release their contents only in the presence of certain trigger molecules associated with cancer [84].

Table 2: Major Technologically Important Factors

Factor	Application	Small angle neutron scattering	Small angle neutron scattering	Transmission electron microscopy
Segment Distribution	Solubilization	+	++	+
Type of Branching	Major cost Diffferences	+	+	+
Terminal Group location	Attachment Networks	++	+	-
Dendrimer-dendrimer Interactions	Ordering Nanostructures	+	++	+
Size Variation With solvent	Standards Release	+	+	-

Key to symbols: ++, best technique for measurement: +, acceptable technique for measurement: -, unsuitable for measurement.

The star polymer gave the most promising results regarding cytotoxicity and systemic circulatory half-life (72 h). With the improvement of drug properties such as plasma circulation time and solubility, 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 [72]. Therefore, the anticancer drug doxorubicin was covalently bound to this carrier via an acid-labile hydrazone linkage. Hence the drug doxorubicin was successfully taken up by several cancer cell lines at reduced cytotoxicity. The studies on adriamycin and methotrexate anticancer drugs on the encapsulation behavior of these demdrimers shows that the highest encapsulation efficiency, with on average 6.5 adriamycin molecules and 26 methotrexate molecules per dendrimer, was achieved for the G4 PAMAM terminated with PEG2000 chains. 5-Fluorouracil (5FU) is known to have remarkable antitumour activity, but it has high toxic side effects. PAMAM dendrimers after acetylation can form dendrimer-5FU conjugates . The dendrimers are water soluble and hydrolysis of the conjugates releases free 5FU. The slow release reduces 5FU toxicity. Such dendrimers seem to be potentially useful carriers for antitumour drugs. The anticancer drug 5-fluorouracil encapsulated into G4 PAMAM dendrimers with carboxymethyl PEG5000 surface chains showed a reasonable drug loading with reduction in the release rate and hemolytic toxicity compared to the non-PEGylated dendrimer[88]. In contrast, up to 24 drug molecules were encapsulated into the hyper branched polyol and successful delivery of the drug into lung epithelial carcinoma cells was achieved by the dendrimers. Recent studies shows that low generation PAMAM dendrimers using Caco-2 cell lines cross cell membranes mostly by a combination of two processes, i.e., paracellular transport and adsorptive endocytosis, while cell efflux systems have a minor effect.[85] The encapsulation of anticancer drugs methotraxate and 5-fluorouracil into PEGylated generation 3 and 4 PAMAM dendrimers

3. DENDRIMER AS SOLUBILITY ENHANCERS

Poly(lysine) dendrimers attached with sulfonated naphthyl groups as antiviral drugs seems to be effective against the herpes simplex virus which can potentially decrease the transmission of HIV and other sexually transmitted diseases (STD) [88]. Studies also show that when PAMAM dendrimer surface is covalently modified with naphthyl sulfonate residues it shows antiviral activity against HIV. This dendrimer based nano-drug can thus inhibit the early stages of virus cell adsorption and later stages of viral replication by hindering the reverse transcriptase and/or integrase enzyme activities. PPI dendrimers modified with tertiary alkyl ammonium groups at the surface is found to be an effective antibacterial biocide against Gram positive and Gram negative bacteria. Poly (lysine) dendrimers with mannosyl groups attached to the surface found to be potent inhibitors of the E. coli adhesion to horse blood cells in a haemagglutination assay, making these structures potential antibacterial agents. Chitosan dendrimer hybrids reveal to act as promising carriers in the field of drug delivery systems, antibacterial agents and in other biomedical applications.

4. CELLULAR DELIVERY USING DENDRIMER CARRIERS

Poor solubility of drugs in pharmaceutically acceptable solvents restricts their use for therapeutic purposes even with their strong therapeutic activity. But now water soluble dendrimers are able to bind and solubilize small acidic hydrophobic molecules with antibacterial properties or antifungal. Unimolecular micelles are Dendrimers with a hydrophobic core and a hydrophilic surface layer..As dendrimers don't have a critical micelle concentration it gives an opportunity for poorly soluble drugs to solubilise by encapsulating them within the dendritic structure at all concentrations of dendrimer. A hydrophilic and hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-flurouracil, a water-soluble anti-tumor drug [86]. It was seen that the oral bioavailability in rats of 5-flurouracil was doubled compared to free 5-flurouracil when the dendrimer fatty acid macromolecule was given with phospholipid coating. Thus Dendrimer-based carriers can be a promising method to enhance the oral bioavailability of poorly soluble drugs.

5. DENDRIMERS AS NANO-DRUGS

he studies on dynamics of cellular entry into A549 human lung epithelial carcinoma cells with a range of PAMAM dendrimers (G4-NH2, G3-NH2, G4-OH, PEGlayted G3 [G3-PEG]) and a hyper branched polymer (polyol) showed that G4-NH2and G4-OH dendrimers entered cells more rapidly than G3-NH2, polyol or G3-PEG. The rapid entry of G4-NH2~ into the cells might be due to its cationic nature of the amine surface groups, that may interact electrostatically with negatively charged epithelial cells and enter by pinocytosis [88]. Absence of cationic surface groups on polyol and G3-PEG, their cellular entry occurs by non-specific adsorption to the cell membrane and subsequent endocytosis. It's also seen that dendrimers can efficiently carry the complexe drugs to the interior of the cells for example

Dendrimer ibuprofen complexes can enter more rapidly into the ceels than the pure drug (1 hr versus > 3 hr).

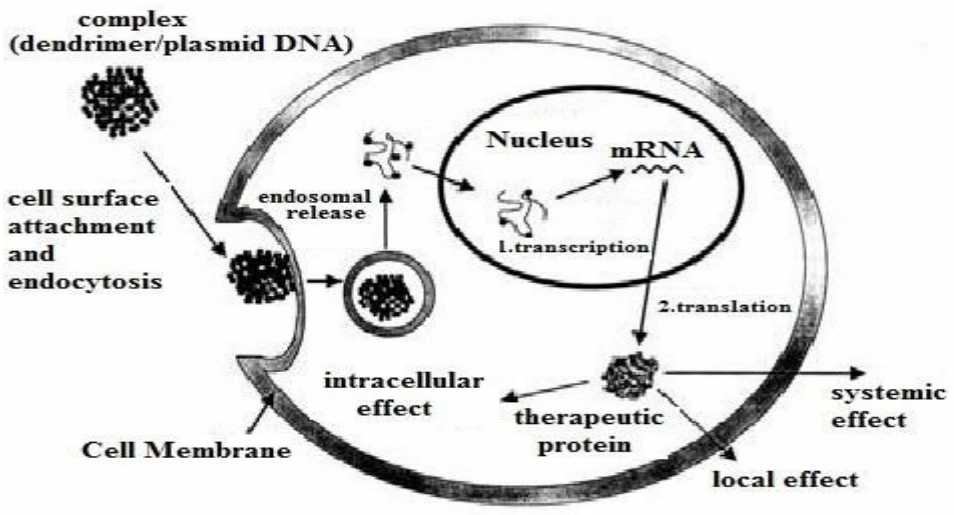
6. DENDRIMERS IN PHOTODYNAMIC THERAPY

Scientists have also studied the use of dendrimers in the sensor technologies. By attaching The photosensitizer 5-aminolevulinic acid to the surface of dendrimers it can be used as an agent for PDT of tumorigenic keratinocytes .The photo sensitive dyes incorporated into dendrimers are utilized in PDT devices[88]. For cancer treatment the light activated photosensitizing drug administered which selectively concentrates in diseased tissue. Appropriate unfunctionalisation of dendrimers can make them a promising carrier for photosensitizers for example ALA a natural precursor of the photosensitizer protoporphyrin IX (PIX) administered to increase cellular concentrations of PIX [87].

7. DENDRIMERS IN GENE TRANSFECTION

In the field of gene therapy dendrimers can act as vectors for example PAMAM dendrimers that has been tested as carriers for the genetic material. Numerous reports reveals that to enhance the transfection of DNA into the cell nucleus by endocytosis can be enhanced by using amino-terminated PAMAM or PPI dendrimers as non-viral gene transfer agents[88]. A transfection reagent called SuperFectTM that have activated dendrimers can carry a larger amount of genetic material compared to viruses. SuperFect-DNA complexes have high stability and provide more efficient transport of DNA into the nucleus than liposomes. The cause for this high transfection efficiency of dendrimers may be due to their well-defined shape and 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. Luciferase gene expression shown by PAMAM dendrimers functionalized with cyclodextrin seems to be 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and cyclodextrin. Better gene delivery process was shown by dendrimers with high structural flexibility and partially degraded high generation dendrimers[93] (i.e., hyper branched architectures) than the intact high generation symmetrical Dendrimers.

Figure 7: Dendrimer involved in gene transfection



ENCAPSULATION OF DRUGS INTO DENDRIMERS ARCHITECTURE

Table 3: Major Technologically Important Factors

Drug	Therapeutic activity	Nature of drug	Inference
Artemether	treat multi-drug resistant strains of malaria	Poor solubility	Solubility enhancement between factors 3-fold to 15-fold has been observed, depending on concentration and size of the dendritic micelles.
Camptothecin	anticancer drug that damages DNA, leading to cell destruction	very low water solubility and adverse side effects	A newly developed dendrimer platform, consisting of poly(etherhydroxylamine) (PEHAM) dendrimers, has been employed to enhance the water solubility of camptothecin [89].
Cisplatin	The anticancer drug that alters DNA structure that prevents replication and initiates apoptosis	The therapeutic effect of cisplatin is limited by its poor water solubility (1 mg/ml), low lipophilicity, and the development of drug resistance	Encapsulation of cisplatin within PAMAM dendrimers resulted in complexes with slower release, higher accumulation in solid tumors, and lower toxicity than free cisplatin.
Diclofenac and mefenamic acid	reduce inflammation and act as analgesic		non-steroidal anti-inflammatory drugs (NSAIDs) have been encapsulated into dendrimers built from citric acid-poly(ethylene glycol)- citric acid triblock copolymers.
Diflunisal	generic NSAID	Low solubility	significantly enhanced permeation of diflunisal, extremely low water solubility of these NSAIDs has been significantly improved by PAMAM dendrimers
Dimethoxycurcumin	ability to induce apoptosis in cancer cells without cytotoxic effects on healthy cells	Poorly soluble in water.	For improved water solubility, dimethoxycurcumin has been mixed with PAMAM dendrimers
Doxorubicin	to treat some leukemia, Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma, and multiple myeloma	Reduced solubility and has side effects	doxorubicin has been encapsulated into PAMAM dendrimers G3 and G4, which had PEG-monomethyl ether chains of molecular weights 550 and 2000 Da conjugated to their surfaces
Etoposide	treatment of malignancies such as Ewing's sarcoma, lung cancer, testicular cancer, lymphoma, non-	Poor water soluble	In order to increase the water solubility of etoposide, micelles composed of block copolymers, lipophilic

	lymphocytic leukemia, and glioblastoma multiform		poly(e-caprolactone) (PCL) and hydrophilic PEG5000, conjugated to a generation two PAMAM-OH dendrimer as the core, have been synthesized.
5-Fluorouracil	5-Fluorouracil (5-FU; Fig. 4) is a pyrimidine analogue that belongs to the family of drugs called antimetabolites	Poorly soluble	A conjugate between PAMAM G4 dendrimer and PEG5000 chains has been utilized in order to improve the solubility of fluorouracil
Ketoprofen	It belongs to the propionic acid class of NSAIDs with analgesic and antipyretic effects.	Poor solubility and bioavailability	The presence of PAMAM dendrimers enhanced the transdermal delivery of ketoprofen, leading to 2.73-fold higher bioavailability compared to suspensions of the pure drug [90]. The solubility of ketoprofen was significantly enhanced by association with PAMAM dendrimers.
Ibuprofen	NSAID, analgesic and anti-inflammatory activity	Less soluble	solubility of ibuprofen can be significantly enhanced by encapsulation into PAMAM dendrimers
Indomethacin	Indomethacin (Fig. 5) is a member of the arylalkanoic acid class of NSAIDs	Indomethacin is poorly soluble in water and sparingly soluble in alcohol	Formulating indomethacin with PAMAM dendrimers G4 with amino, hydroxyl, and carboxylate surface groups enhanced the water solubility of the drug
Methotrexate	an antimetabolite and antifolate drug used in the treatment of many cancers, acts by inhibiting the metabolism of folic acid.	higher doses of MTX often used in cancer chemotherapy can cause toxic effects to the rapidly dividing cells of bone marrow and gastrointestinal mucosa.	methotrexate has been encapsulated into generations 3 and 4 PAMAM dendrimers, which had PEG550 and PEG2000 monomethyl ether chains conjugated to their surfaces to modify bioavailability and toxicity.
Naproxen	used for the reduction of moderate to severe pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis and others.	Low soluble	the solubility of naproxen was significantly enhanced by the association with PAMAM dendrimers
Niclosamide	antimicrobial drug	Niclosamide is practically insoluble in water at physiological pH and becomes sparingly soluble over the range of pH 8–10	mixing with PAMAM dendrimers (8.0 mM) containing a primary amine surface significantly enhanced the water solubility of niclosamide
Nifedipine	The NSAID nifedipine is a dihydropyridine calcium	Poorly solubility	the solubility of nifedipine increased with the size of the

	channel blocker.		dendrimers. PAMAM dendrimers enhanced the release rate of nifedipine, dependent on dendrimer size and concentration.
Quinolones nadifloxacin and prulifloxacin	Quinolones are a family of broad-spectrum antibiotics covering a host of aerobic Gram-negative, Gram-positive and even some anaerobic species responsible for various infections	Low solubility	The solubility of nadifloxacin and prulifloxacin was significantly enhanced in formulations containing PAMAM dendrimers G3–5 with amine surface,
Paclitaxel	anticancer drug	poor water soluble	PTX encapsulation into polyglycerol dendrimers resulted in 400-fold improved water solubility compared to the pure drug [91].
Silver salts	antimicrobial activity		The encapsulation of silver salts within PAMAM dendrimers produced conjugates exhibiting slow silver release rates and antimicrobial activity against various Gram-positive bacteria [92].
Sulfamethoxazole	sulfonamide antibacterial drug	SMZ is sparingly soluble in water, causing problems in its clinical applications.	Association with PAMAM dendrimers G2-4 in low (3–9 mM) concentration range enhanced the aqueous solubility of sulfamethoxazole linearly with the dendrimer concentration. SMZ–PAMAM complexes increased the antibacterial activity

CONCLUSION

The dendrimers can have a promising future in various pharmaceutical and diagnostic fields as they possess distinct properties such as multivalenc, high degree of branching, globular architecture and well-defined molecular weight, thus presenting new scaffolds for drug delivery. The increasing challenges of newly developed drugs such as poor solubility, bioavailability and permeability can be resolved with the help of dendrimers. The advancement in synthesis of dendrimers help to produce different structure at low cost and careful surface engineering can eliminate the problem of biocompatibility and toxicity. Hence the increased research in the field of dendrimers promises its utility for wide range of application in drug delivery systems.

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