Journal of Applied Pharmaceutical Research 2016, 4(1): 01 – 19

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH

ISSN No. 2348 – 0335 **www.japtronline.com**

DENDRIMERS: NOVEL CARRIERS FOR DRUG DELIVERY

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Article Information

Received: 11th December 2015

Revised: 25th December 2015

Accepted: 12th January 2016

Keywords

Dendrimers, generations, divergent

ABSTRACT

Dendrimers are highly branched, organic compounds with well-defined, symmetrical structure. From chemical point of view they are three-dimensional polymers, characterized by a globular shape. At the end of the arms are terminals, functional groups, which can be easily modified in order to change their chemical and physical properties. Dendrimers have nanoscopic particle size range from 1 to 100 nm. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions, their size is very close to various important biological polymers and assemblies such as DNA and proteins. The structure of dendrimer molecules begins with a central atom or group of atoms labeled as the "core." From this central structure, branches of other atoms called 'dendrons.' The continuous branching results in layers of branch structure called "generations."Synthesis of dendrimers done by four methods. These are 'Divergent' Dendrimer Growth , 'Convergent' Dendrimer Growth ,'Double Exponential' and 'Mixed' Growth ,'Click' Synthesis (Hypercores and branched monomers growth). Mechanisms of drug loading onto dendrimer carriers by physical encapsulation of drug molecules and chemical conjugation of drug molecules. The conjugates show increased solubility, decreased systemic toxicity and selective accumulation in solid tumors. Various applications as pharmaceutical and non pharmaceuticals. Dendrimers may have toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity also limitation that does not apply where the drug is solubilised with dendrimer and then released in the gut for absorption. Some Marketed products of dendrimers are available named as Starburst, Priostar, Stratus CS, Vivagel, Alert ticket, SuperFect, Taxotere.

INTRODUCTION

Dendrimers are highly branched, organic compounds with well-defined, symmetrical structure. From chemical point of view they are three-dimensional polymers, characterized by a globular shape. At the end of the arms are terminals, functional groups, which can be easily modified in order to change their chemical and physical properties. There are two types of dendrimer generation – a full generation with hydroxyl or amine surface group and a half generation with carboxyl surface group. The last characteristic elements in the structure of dendrimers are internal cavities – the empty spaces, which can be used as a "pocket" for different kind of small particles[1].

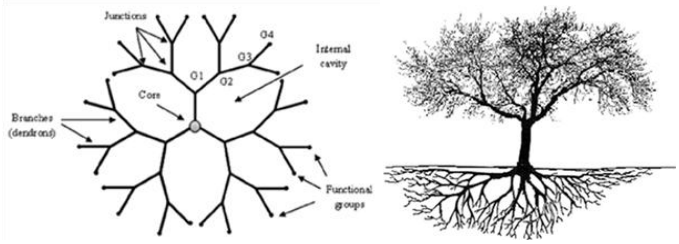

Fig.1 Schematic description of dendrimer structure

Dendrimers have often been referred to as the "Polymers of the 21st century". The word "dendrimer" originated from two words, the Greek word Dendron, meaning tree, and meros, meaning part (Fig.1). At the same time, Newkome's group, independently reported synthesis of similar macromolecules.

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They called them arborols from the Latin word 'arbor' also meaning a tree. The term cascade molecule is also used, but 'dendrimer' is the best established one[2].

Advantages of Dendrimers

Dendrimers offers various advantages over other polymers:

a. Dendrimers have nanoscopic particle size range from 1 to 100 nm, which makes them less susceptible for RES uptake.
b. Due to stringent control during synthesis, they have lower polydispersity index. As the density of branches increases the outer most branches arrange themselves in the form of spheres surrounding a lower density core and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment.
c. Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body.
d. Dendrimers can be modified as stimuli responsive to release drug.
e. Dendrimers might show an enhanced permeability and retention effect (depending on their M.W) that allows them to target tumor cells more effectively than small molecules.
f. The advantage of dendrimers is that they can be synthesized and designed for specific applications. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins which are physiologically ideal.
g. Medication to the affected part inside a patient's body directly.
h. In target drug delivery: Dendrimers are suitable for targeting solid tumours due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumour (enhanced permeation rate). There is also reduction in amount of drug multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components[3-5].

History of dendrimers

During the 20th century, at least six major technological movements emerged and evolved into mature disciplines that have revolutionized scientific thinking, enhanced the prosperity of many countries, and dramatically improved the human condition. They have been referred to as major technological ages and, in approximate chronological order, are recognized as the chemical, nuclear, plastics, materials, biotechnology, and computer ages. An apparent driving force behind each technological age has been the quest for "new properties".

Table 1. Early Peer-Reviewed Publications on Dendritic Molecules (1978–1991)

Year	Lead Authors	Working
1978	Voegtle	PAMAM dendrimers with molecular weights ranging from several hundred to over 1 million daltons (i.e., generations 1–13) were prepared in high yields.
1983	de Gennes	Predicted fundamental dendrimer surface congestion properties
1985-1990	Newkome/ Baker	initial presentation of convergently grown dendrimers was made
1985-1990	Tomalia/ Turro/ Goddard	There was an enormous amount of intrinsic interest in dendritic polymer architecture.
1990-1991	Fre´chet/ Hawker	Demonstrated the versatility of the convergent method with the preparation of dendrimers having differentiated functionalities[6-20].
1990	Miller/ Neenan *random hyper branched polymers*	The convergent synthesis of an aromatic polyester was reported.
1990	Kim/ Webster	The rate of publication of dendrimer articles began to climb markedly while there were still only three articles on random hyper branched polymers.
1991	Tomalia	Articles on dendrigraft polymers.
1991	Gauthier/ Mo¨ller	Articles on Arborescent polymers.

Properties of dendrimers

1. Dendritic polymers that can be constructed with a well-defined molecular structure, i.e. being mono-disperse, unlike to linear polymers.
2. Nanoscale sizes that have similar dimensions to important bio-building blocks, e.g., proteins, DNA.

3. When dendrimer surfaces modified with small functional groups or polyethylene glycol (PEG) show non or low immunogenicity.
4. Ability to arrange excretion mode from body, as a function of nanoscale diameter.
5. An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties, reduces the drug toxicity and facilitates controlled release.
6. Numbers of terminal surface groups suitable for bioconjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.
7. Surfaces that may be designed with functional groups to resist trans-cellular, epithelial or vascular bio permeability.
8. Dendrimers are monodisperse macromolecules. Size and molecular mass of dendrimers can be specifically controlled during classical polymerization process.
9. When the molecular mass of dendrimers increases, their intrinsic viscosity goes through a maximum at the fourth generation and then begins to decline.
10. The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity.
11. Dendrimer solubility is strongly influenced by the nature of surface groups.
12. The dendrimer should be: nontoxic, on-immunogenic, able to cross bio barriers (biopermeable), able to stay in circulation for the time needed to have a clinical effect and able to target to specific structures[21 , 22].

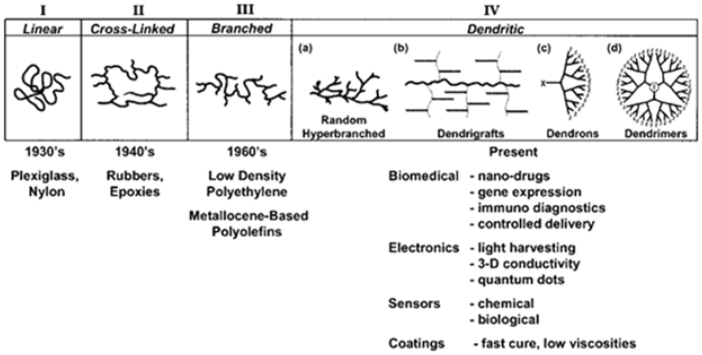

Fig. 2 Representation of the four major classes of macromolecular architectures

TYPES OF DENDRIMERS

Physical type of dendrimers

a) PAMAM Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core.

b) PAMAMOS Dendrimers

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 honey comb like networks with nanoscopic PAMAM & OS domain.

c) PPI Dendrimer

PPI-dendrimers stand for "Poly (Propylene Imine)" 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).

d) Tecto Dendrimer

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

e) Chiral Dendrimers

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

f) Hybrid Dendrimers Linear Polymers

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

g) Amphiphilic Dendrimers

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

h) Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

i) Multiple Antigen Peptide Dendrimers

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

j) Frechet-Type Dendrimers

It is a more recent type of dendrimer developed by Hawker and Frechet 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[23-27].

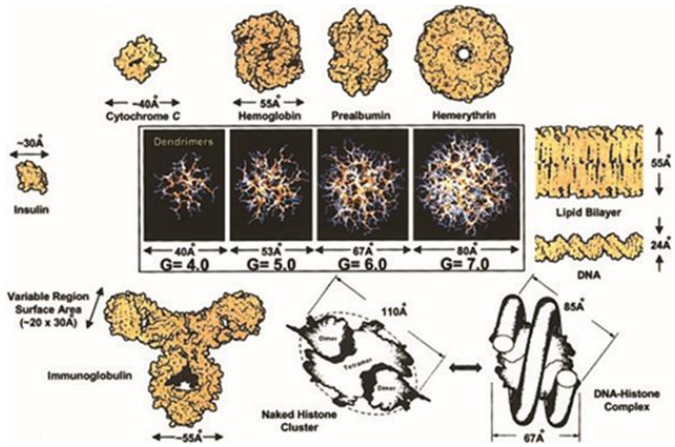

Fig. 3 Dimensionally scaled comparison of series of PAMAM dendrimers (NH3 core; G 4–7) with a variety of proteins, a typical lipid-bilayer membrane & DNA, indicating closely matched size & contours of important proteins & bioassemblies

Chemical types of dendrimers

1. Simple Dendrimer

They have simple monomer units. Convergent synthesis of sequence of monodisperse are lester dendrimer, based upon symmetrically substituted benzene tricarboxylic acid ester is described. These materials consist of 4, 10, 22 & 46 benzene rings linked symmetrically & have molecular diameters of 45A.

2. Liquid crystalline dendrimer

These are made of mesogenic monomers e.g. mesogen functionalized carbosilane dendrimer.

3. Chiral dendrimer

Chirality is based on the building of 4 constitutionally assorted but chemically alike branches to an achiral core e.g. chiral dendrimers obtained from pentaerythritol

4. Micellar dendrimer

These are unimolecular micelle arrangement dendrimers. Fully aromatic, water soluble dendrimers forming a collection of aromatic polymeric chain which able to generate an environment that resembles some micellar structures, which forms complex with small organic molecules in water.

5. Hybrid dendrimers

These are the preparation of dendritic and linear polymer in hybrid block or graft copolymer form. e.g. hybrid dendritic linear polymers.

6. Amphiphilic dendrimer

These are the class of globular dendrimers that have asymmetrical but highly controlled division of chain end chemistry. These may be oriented at interface forming interfacial liquid membranes for neutralizing aqueous organic emulsion

7. Metallo dendrimer

Dendrimers attached with the metal ion to form the complexation either in the interior or on the peripheral, which may be regarded as metallodendrimers. The ruthenium bipyridine complex based dendrimer have attribute electrochemical and luminescence properties[28].

Table. 2 Properties of dendrimers

Property	Dendrimers	Linear Polymers
Structure	Compact, Globular	Not compact
Synthesis	Careful & stepwise growth	Single step polycondensation
Structural control	Very high	Low
Architecture	Regular	Irregular
Shape	Spherical	Random coil
Crystallanity	Non-crystalline, amorphous materials -lower glass temp.	Semicrystalline/crystalline materials -Higher glass temperatures
Aqueous solubility	High	Low
Non-polar solubility	High	Low
Viscosity	Nonlinear relationship with molecular weight	Linear relation with molecular weight
Reactivity	High	Low
Compressibility	Low	High
Polydispersity	Monodisperse	Polydisperse

STRUCTURE OF DENDRIMERIC MOLECULE

The structure of dendrimer molecules begins with a central atom or group of atoms labeled as the core. From this central structure, branches of other atoms called 'dendrons' grow through various chemical reactions. The continuous branching results in layers of branch structure called "generations." Another way to determine the generation of a dendrimer is through the total number of focal or branching points (from the core to the surface) that it has. For example, a dendrimer with 4 focal points would be a fourth generation dendrimer, labeled as G4. There is a myriad of generations, ranging from just a few to hundreds or even thousands. As the molecule grows bigger, the structure becomes denser and more tightly packed. Eventually, the branches cannot grow any further because there is no room. The generation at which this occurs is different for every molecule, but it is known as the starburst effect. The shape of lower generation molecules (such as G0, G1, and G2), tend to be asymmetrical, but as the generation number increases, the structure becomes more spherical. Other components of dendrimers include the shell (segment between focal points), and the end-group (the atoms that make up the surface of the molecule).

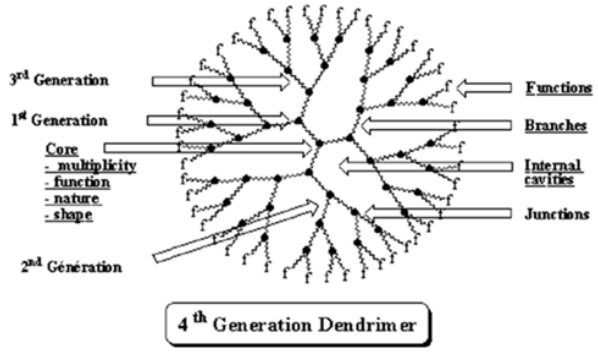

Fig. 4 Generations of Dendrimers

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 the process repeats, successive layers are added and the sphere can be expanded to the desired size by the investigator. The final entity is spherical macromolecular structure whose size is similar to blood albumin and hemoglobin.

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 is also generally referred to as the "terminal group" or the "surface group" of the dendrimer. Dendrimers having amine end-groups are termed "aminoterminated dendrimers".

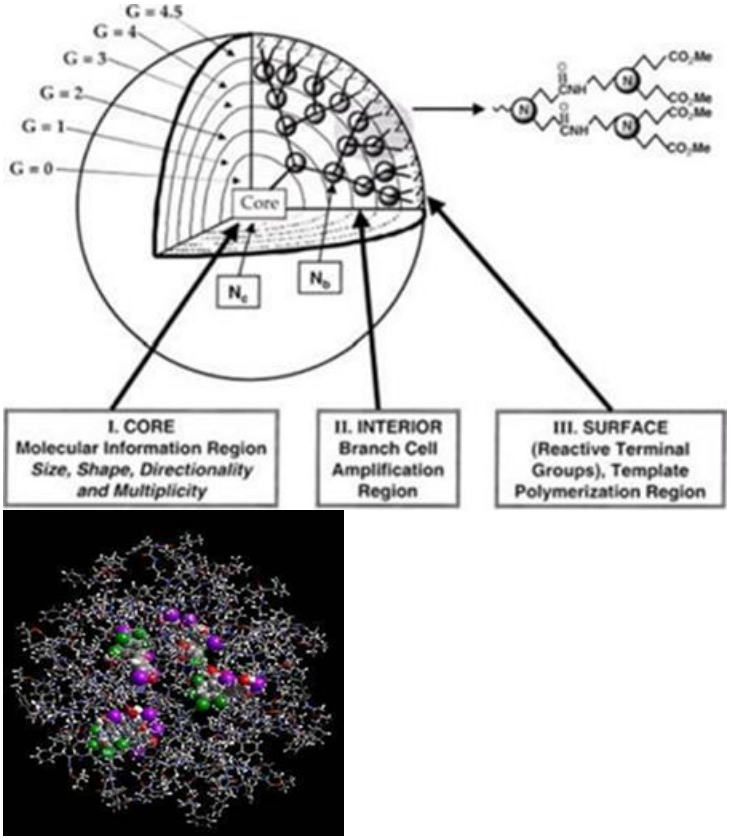

Fig. 5 Three dimensional projection of dendrimer core-shell architecture for G=4.5 PAMAM dendrimer with principal architectural components (I) core, (II) interior & (III) surface.

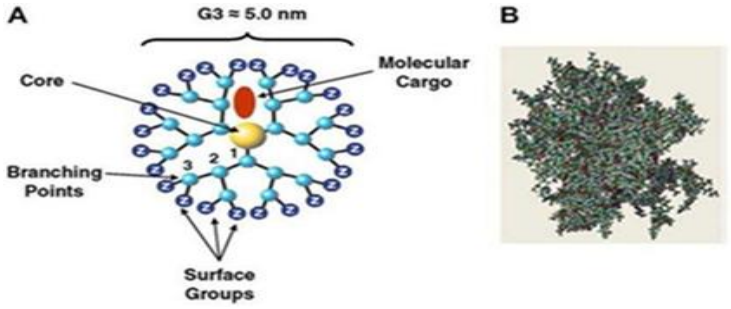

Fig. 6 (A) 2D Representation of dendrimers demonstrating its different components **(B)** 3D Representation of dendrimers

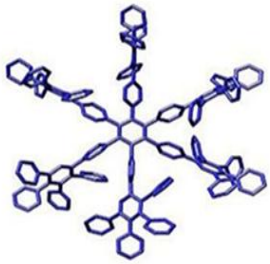

Fig. 7 PAMAM dendrimer crystal structure of 1st generation polyphenylene dendrimer.

COMPONENTS OF DENDRIMERS

a. Generation

It is the hyper branching 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 going from the core towards the dendrimer surface is the generation number.

Dendrimer having five focal points when going from the centre to the periphery is denoted as the 5th generation dendrimer and 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 as generation "zero", or in terminology as "G0". The core structure thus presents no focal points as hydrogen substituent's are not considered focal points. Intermediates during the dendrimer synthesis are sometimes denoted as half-generations; a well-known example is the carboxylic acid-terminated [29 , 30]

b. Shell

The dendrimer shell is the homostructural spatial segment between the focal points. The "outer shell" is the space between the last outer branching point and the surface. The "inner shells" are generally referred as the dendrimer interior.

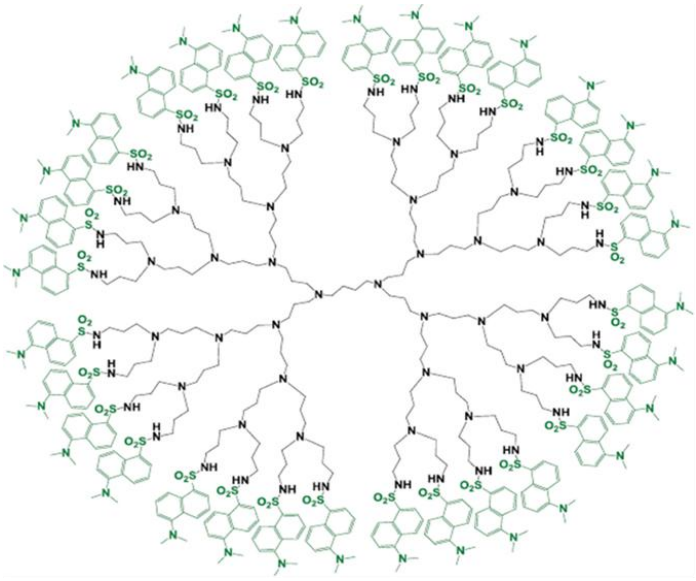

Fig. 8 Structure of Poly propylene amine

c. Pincer

In dendrimer, 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 dendrimer the number of pincers is half the number of surface groups (because in these dendrimers chain divides into two in each focal point).

d. 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".

SYNTHESIS of dendrimers

'Divergent' Dendrimer Growth

This name comes from the way in which the dendrimer grows outwards from the core, diverging into space. Divergently grown dendrimers are virtually impossible to isolate pure from their side products. The first synthesized dendrimers were polyamidoamines (PAMAMs). Divergent synthesis is initiated with a multifunctional core molecule like ethylenediamine (EDA), then with the help of Michael addition reaction four arms are added on nitrogen of EDA (two arms possible on each nitrogen), after this in second step EDA is again reacted on these formed four arms through amidation reaction as shown in following diagram These two steps can be repeated multiple times to formdifferent generations of dendrimers, in each generation number of arms doubles from previous generation.

To avoid structural defects at higher generations a large excess of Michael donor (EDA) is used in this approach. This divergent route is advantageous to get higher yield ofdendrimer with lower purity or we can say that purity is compromised for getting higher yield. That's why this approach of synthesis is very useful and used worldwideat commercial scale for production of dendrimers. Lesser purity in divergent synthesis of dendrimers. Lesser purity in divergent synthesis of dendrimers is basically due to missing repeat units

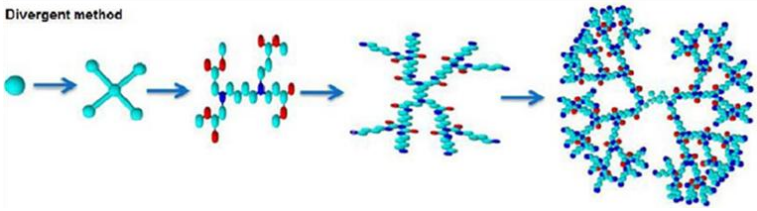

Fig. 9 Synthesis by Divergent method

'Convergent' Dendrimer Growth

The 'convergent' approach was developed as a response to the weaknesses of divergent syntheses. 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. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step.

a. Relatively easy to purify the desired product and the occurrence of defects in the final structure is minimised.

b. Possible to introduce subtle engineering into the dendritic structure by precise placement of functional groups at the periphery of the macromolecules.

c. Approach does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule.

d. Convergent approach of dendrimer synthesis overcomes the purity and structural defect issues of divergent synthesis. By this approach more uniform and symmetric dendrimers can be synthesized but with lower overall yield. In other words yield is sacrificed for purity and this approach is generally used for laboratory scale dendrimer synthesis. For commercial scale production, divergent synthesis is still favored. Most commonly used commercially available dendrimers are PAMAM and PPI, which are structurally somewhat different in every batch due to structural defects.

e. Convergent approach of dendrimer synthesis was first introduced by Jean Frechet. In this approach dendrons that ends up to terminal groups are synthesized first and in final step these are linked together to a core molecule for getting complete dendrimer structure as shown in figure10. Dendrimers synthesized by this way have less impurities, more monodispersity and symmetry because better purification is possible of dendrons before final attachment to core.

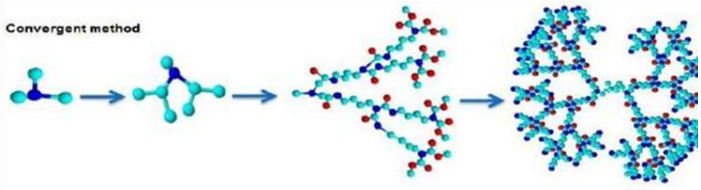

Fig. 10 Synthesis by Convergent method

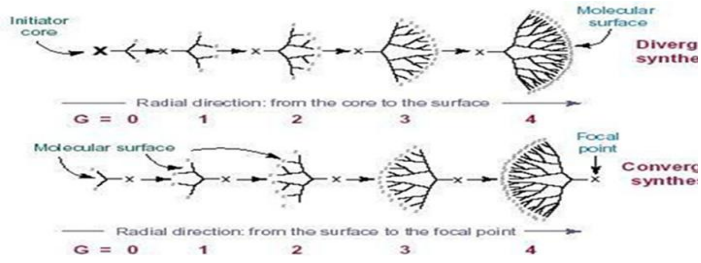

Fig. 11 Divergent & convergent method of dendrimer synthesis

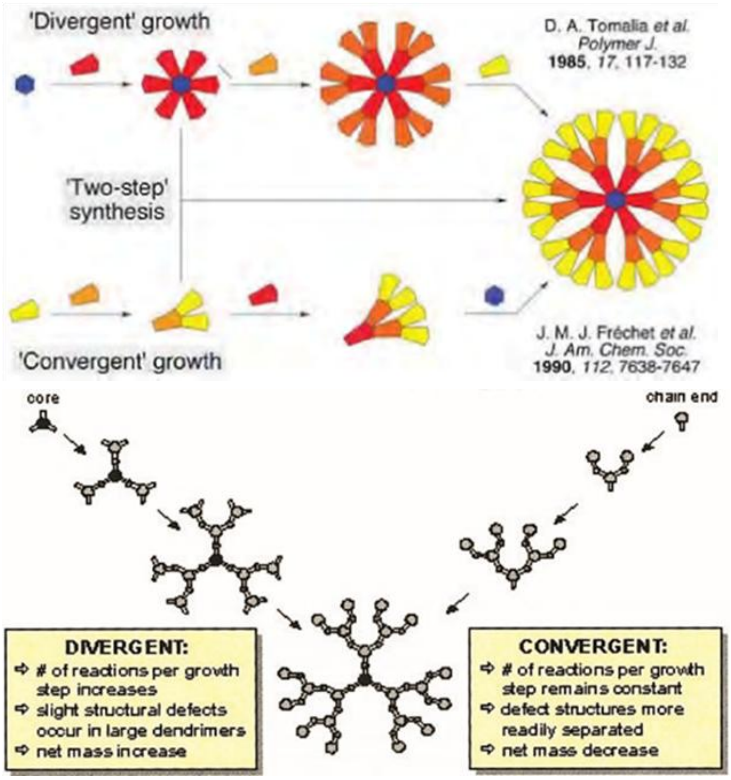

Fig. 12 Divergent & convergent method of dendrimer synthesis

'Double Exponential' And 'Mixed' Growth

The most recent fundamental breakthrough in the practice of dendrimers synthesis has come with the concept and implications of 'double exponential' growth. A schematic representation of double exponential and mixed growth. This approach allows the preparation of monomers for both convergent and divergent growth froma single starting material. These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again[31].

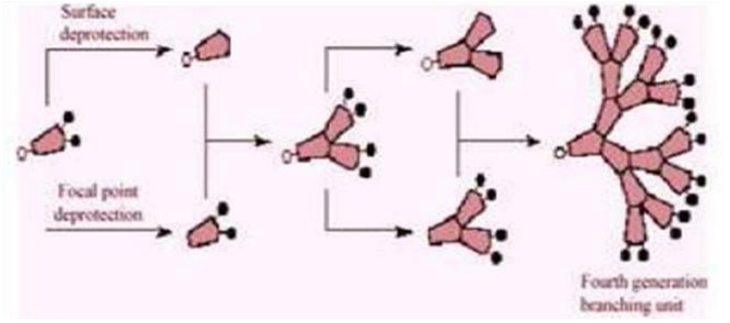

Fig. 13 Double exponential growth

'Click' Synthesis

"Click" chemistry refers to Cu-catalyzed cycloaddition reaction of an alkyne and an azide to form a 1,2,3-triazole ring. The coupling specificity, mild reaction conditions, and

quantitative synthetic yields of click reactions motivated the synthesis of dendrimers using this method.G3 triazole dendrimers were synthesized using a branched alkyne monomer with an alkyl chloride focal point.Using the convergent approach, dendrons are synthesized by triazole formation with the peripheral monomer alkynes followed by conversion of the focal point to an azide functionality for reiterative monomer addition (Figure 14). Coupling of the dendrons to a polyacetylene core produced G3 triazole dendrimers with a 92% yield after simple aqueous workup and filtration to remove the NaCl byproduct. It is important to note that "clicked" dendrons can be used to produce symmetricand asymmetric PAMAM This method involved the pre-assembly of oligomeric species which can be linked organic methodologies. [32-36]

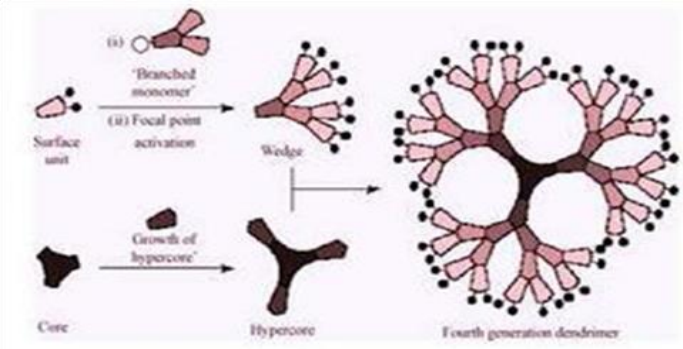

Fig. 14 Hypercores and branched monomers growth

MECHANISMS OF DRUG LOADING ONTO DENDRIMER CARRIERS

Physical Encapsulation of Drug Molecules

The work of Vogtle and co-workers, who looked at entrapment of guest molecules into branched polymers,1 represents an earlier form of physical encapsulation of poorly soluble drug molecules in dendrimer's voids to improve their aqueous solubility and control their release profile Inclusion of hydrophobic molecules into dendrimers is typically accomplished by simple mixing of the polymer and drug solutions where the hydrophobic drug associates with the nonpolar core through hydrophobic intereactions. As a result of this physical interface between the guest molecules and the dendrimer carrier, release of the encapsulated molecules in an aqueous environment is passively controlled by a range of noncovalent interactions including hydrophobic forces, hydrogen bonding, steric hindrance, and electrostatic interactions. To maximize the loading capacity of drug molecules within the dendrimer, one has to carefully consider polymer architecture, specifically the characteristics of the internal voids. Initial computational and experimental studies by Goddard and Tomalia showed that G1-G3 -alanine dendrimers exhibit an oblong open structure while G4 and higher generations possess a densely packed surface that is necessary to produce enclosed internal voids that can effectively encapsulate and retain guest molecules. Spin-lattice relaxation profiles of acetyl salicyclic acid and 2,4-dichlorophenoxy acetic acid encapsulated within a dendritic carrier displayed a decline in carbon-13 relaxation time with increasing dendrimer's generation number from G0.5-G5.5, thus indicating the shielding of the guest molecules in the polymer network. These findings set the stage for development of different inclusion complexes where dendrimers can encapsulate hydrophobic anticancer drugs to improve their aqueous solubility, control their release rates, and achieve cancer therapy.

Fig. 15 Drawing of a dendrimer carrier encapsulating hydrophobic drug molecules in the dendrimer's voids to increase their aqueous solubility and control their release rate

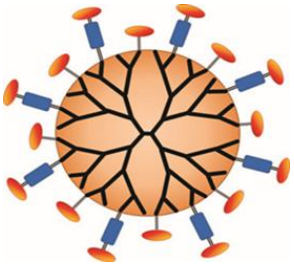

Fig. 16 Schematic drawing showing a Dendrimer drug conjugate where the drug molecules (red ovals) are either directly coupled (solid lines) dendrimer's surface groups or via pH sensitive linkage (blue rectangle)

The well defined 3D structure and many functional surface groups, drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups (as shown in the figure). Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug).[37-39]

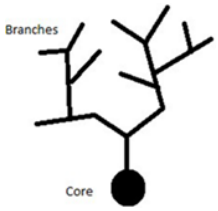

Fig. 17 Structure of Dendrimer at terminal surface of branches

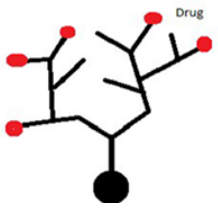

Fig. 18 Dendrimer molecule with drug molecules loaded within branches

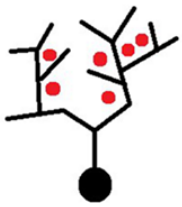

Fig. 19 Dendrimer molecule with drug molecules encapsulated

There are broadly two mechanisms for drug delivery :-

A) First, is by in vivo degradation of drug dendrimer conjugate (covalent bonding of drug to dendrimer), which depends on presence of suitable enzymes or an environment capable of degrading bonds.

B) The second one is by releasing the drug due to changes in physical environment such as pH, temperature. This approach is independent of the external factors and takes place in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor).[40]

Chemical Conjugation of Drug Molecules

a. Direct Coupling

In the early 1990s, Barth and co-workers conjugated boronated monoclonal antibodies to a dendrimer carrier via stable urea linkages and utilized this conjugate for neutron capture therapy where localized neutron ionization would cause necrosis of neighboring cancer cells.113,139 This conjugate achieved high loading capacities of 250-1000 boron atoms per G4 dendrimer while retaining 82% of the antibodies activity in vitro. A few years later, Duncan and coworkers reported the coupling of cisplatin (Pt), a hydrophobic DNA intercalating agent, to G3.5 PAMAM dendrimers via an ester linkage.140 PAMAM-Pt conjugates carried 20-25 weight % platinum exhibiting 10-fold higher aqueous solubility compared to free Pt and displayed great stability (<1% Pt release) upon incubation in PBS (pH 7.4) and citrate buffers (pH 5.5) at 37 °C for 72 h.140 Despite the high aqueous solubility and stability of these conjugates, they failed to produce the desired anticancer activity due to limited drug release.

b. pH-Sensitive Linkages

The desire to achieve cancer cell-specific delivery and release of anticancer drugs motivated the development of dendrimer-drug conjugates with hydrolyzable linkages. Specifically, the sought linkages had to remain intact in the systemic circulation but quickly degrade once internalized into the cancer cell and release the attached drug to produce the desired therapeutic activity. The incorporation of pH sensitive linkages into dendrimer-drug conjugates seemed to fit the desired criteria as they remain stable in the systemic circulation (pH 7.4) but quickly hydrolyze in acidic environment (pH 5-6) like the endosomes/lysosomes, thus releasing the incorporated drug inside the target cell. While these pH-sensitive linkages represent a significant improvement over non cleavable conjugates for intracellular drug delivery of anticancer drugs, they only sense the acidity of the endosomal compartment but fail to differentiate between cancer cells and normal healthy ones.

Therefore, further selectivity of drug release from dendrimer conjugates can be achieved by development of novel chemical linkages that are sensitive to cancer-specific markers such as intracellular enzymes.[41-48]

CHARACTERIZATION OF DENDRITIC POLYMER

A. Spectroscopy and spectrometry methods:-Spectroscopy and spectrometry methods of characterization of dendritic polymer are as follows.

a. Ultra-violet-visible spectroscopy(UV-VIS):-Provides information for monitoring the synthesis of dendrimers. The intensity of the absorption band is basically proportional to the number of chromophoric units.
b. Infra red spectroscopy (IR):-Provides information for routine analysis of the chemical transformations going at the surface of dendrimers.
c. Near infra red spectroscopy:-Provides information for the characterization of delocalize π-π stacking interaction between end groups of modified PAMAM.
d. Fluorescence:-Provides information for increasingly high Sensitivity of fluorescence used to quantify defects during the synthesis of dendrimers.
e. Mass spectroscopy:-Chemical ionization or fast atom bombardment used for the characterization of small dendrimers whose mass is below 3000Da. Electrospray ionization used for dendrimers which are able to form stable multicharged species.
f. X-ray diffraction (XRD):-Provides information to allow precise determination of the chemical composition, structure, size and shape of Dendrimer.

B. Scattering techniques:-Scattering techniques for characterization of dendritic polymer are as follows

a. Small angle X-ray scattering (SAXS):-Provides information about their average radius of gyration (Rg) in solution. The intensity of the scattering also provides information on the arrangement of polymer segments.
b. Small angle neutron scattering (SANS):-Provides access to the radius of gyration, but may also disclose more accurate information than SAXS. The location of the ending groups has also been determined by SANS experiments conducted with PAMAM dendrimers and PPI dendrimers.
c. Laser light scattering (LLS):-It determines the hydrodynamic radius of dendrimers. Dynamic LLS is mostly used for the detection of aggregates.

C. Microscopy methods:- Microscopy methods for characterization of dendritic polymer are,

a. Transmission microscopy:-Electron or light produce images that intensify the original, with a resolution eventually limited by the wavelength of the source.
b. Scanning microscopy:-It produces an image by touch contact Q at a few angstroms of a sensitive canilever arm with sample. Ex. Atomic force microscopy.

D. Size exclusive chromatography:- It allows the partition of molecules according to size.[37]

E. Electrical techniques:- Electrical techniques for characterization of dendritic polymer are as follows

a. Electron paramagnetic resonance (EPR):-Quantitative determination of the substitution effectiveness on the surface of PANAM dendrimers.
b. Electrochemistry:-It provides information about the possibility of interaction of electroactive end groups.
c. Electrophoresis:-It provides the information about the assessment of purity and homogeneity of several types of water soluble dendrimers.

F. Rheology and Physical properties:- Rheology and physical properties used for characterization of dendritic polymer are as follows

a. Intrinsic viscosity:-It is as analytical probe of the morphological structure of dendrimers.
b. Differential scanning calorimetry (DSC):- It used to detect the glass transition temperature depends on thy moleculer weight, entangment and chain composition of polymers.
c. Dielectric spectroscopy (DS):- Gives complete information about molecular dynamic processes (α-, β)

G. Miscellaneous methods:- Other methods used of characterization of dendritic polymer are as follows

a. X-ray Photoelectron Spectroscopy (XPS):-It provides detailed information about chemical composition of dendrimers such as poly (aryl ether) dendrons or PAMAM dendrimers which was obtained using XPS. This technique is most generally used for the characterization of layers.
b. Sedimentation Technique:- Used for lactosylated PAMAM dendrimers, measurements of dipole moments for PMMH dendrimer.
c. Titrimetry:-It is used for determining number of NH2 end groups of PAMAM dendrimers.[49-68]

APPLICATIONS of dendrimers

A. Non-Pharmaceutical Application:

1. Diagnostics
2. Dendritic Catalysts / Enzymes
3. Industrial Processes

B. Pharmaceutical Application:

1. Covalent Dendrimer–Drug Conjugates
2. Noncovalent Encapsulation of Drugs / Host –Guest
3. Delivery of Anticancer Drugs by Dendrimers and Dendritic Polymers
4. Dendrimers Drug Delivery: Targeted and Controlled Release Drug Delivery
5. Dendrimer as Solubility Enhancers
6. Dendrimers in Photodynamic Therapy
7. Dendrimers as Nano-Drugs

C. Miscellaneous Applications of The Dendrimers

D. Current And Potential Applications Of Dendrimers:

A. Non-Pharmaceutical Application

1. Diagnostics

Paramagnetic metal chelates such as Gd(III)-N,N',N'',N'''tetracarboxymethyl-1,4,7,10-tetraazacy-clododecane (Gd(III)DOTA), Gd(III)-diethylene tri- amine pentaacetic acid (Gd(III)DTPA), and their derivatives used as contrast agents for magnetic resonance imaging(MRI). DNA-dendrimers, which are constructed for routine, use in high-

throughput functional genomics analysis, and as biosensors for the rapid diagnosis have genetic, and pathogenesis diseases.

2. 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.

a) Metallodendritic catalysts.
b) Catalysis with phosphine-based dendrimers.
c) Catalysis with (metallo) dendrimers containing chiral ligands.
d) Non-metal containing dendrimers.[69-84]

3. Industrial Processes

Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. Cooper and co-workers synthesized fluorinated dendrimers, which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from water into liquid CO_2.

B. Pharmaceutical Application:

1. Covalent Dendrimer–Drug Conjugates

An alternative approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for the covalent attachment of drug molecules to the dendrimers periphery. In dendrimer–drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids. 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.

2. Non covalent encapsulation of drugs/Host-guest relation

Encapsulation of drugs use the satiric bulk of the exterior of the dendrimer or Interactions between the dendrimer and drug to trap the drug inside the dendrimer. Maciejewski introduced the concept of encapsulating guest molecules into special, egg-shell-like structures. Such a system can be used to encapsulate drugs and provide controlled delivery. For example, in early studies, DNA was complexed with PAMAM dendrimers for gene delivery applications.

3. Delivery of Anticancer Drugs by Dendrimers and Dendritic Polymers

Dendrimer molecule has hundreds of possible sites to couple to an active species. This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells. Poly(amidoamine) (PAMAM) dendrimers are emerging as prospective candidates for efficient targeted drug and peptide delivery system due to their hyperbranched, welldefined globular nanometer-sized, multiple end modifiable groups and high biocompatibility. PAMAM dendrimers have been used for drug delivery platform, by covalently conjugating drug molecules for cancer therapeutics. Conjugation of poor-bioavailable drugs with PAMAM dendrimer increases their bioavailability, and decreases dose frequency. Methotrexate (MTX) conjugated with dendrimer showed 8-fold more toxic effect against resistant human acute lymphoblastoid, as compared to free MTX. It has also been reported that tamoxifen conjugated to PAMAM dendrimer enhances the blood brain barrier (BBB) transportation and improves the drug accumulation in glioma cells. The covalent attachment of drugs on to dendrimer surfaces offers stable dendrimer-drug conjugates. It is necessary to cleave the covalent attachment between drug and dendrimer in order to optimize drug release at the specific biological condition**.** The covalent linkage of the drugs to the surface functional groups of dendrimer can be achieved via ester or amide or disulphide bond, which can be cleaved hydrolytically or enzymatically or via glutathione. [85-92]

4. Dendrimers Drug Delivery: Targeted And Controlled Release Drug Delivery

Dendrimers have attracted attention as possible drug carriers because of their unique properties namely their well defined three dimensional structure, the availability of many functional surface groups, their low polydispersity and their ability to mimic. Drug molecules can be loaded both in the interior of the dendrimers as well as attached to the surface groups. Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug).

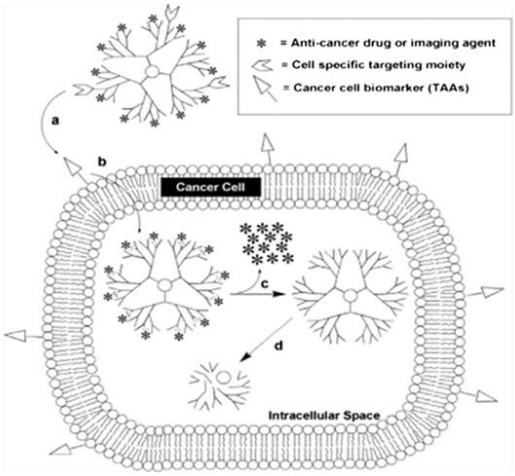

Fig. 20 Cancer targeted drug delivery

a) Dendrimers for controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. drug gives slow and sustained in vitro release, as compared to cellulose membrane control. Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers

b) Dendrimers in targeted drug delivery

Dendrimers have ideal properties which arebrought in application in targeted drug delivery system. One of the most effective cell-specific targetingagents delivered by dendrimers is folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains possessed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer. The star polymer were reported to give 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 tumours. Combined these factors lead to the selective accumulation of macromolecules in tumour tissue, a phenomenon termed the 'Enhanced Permeation and Retention' (EPR) effect. Therefore, the anticancer drug doxorubicin was reported to be 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.

c) Dendrimers in Gene Transfection(For Gene Delivery)

The ability to deliver pieces of DNA to required parts of a cell involves many challenges. Research is being performed to find ways to use dendrimers to traffic genes into cells without damaging or deactivating the DNA. To maintain the activity of DNA during dehydration, the dendrimer-DNA complexes are encapsulated in a water soluble polymer, and then deposited on or sandwiched in functional polymer films with a fast degradation rate to mediate gene transfection.[93] Based on this method, PAMAM dendrimer-DNA complexes were used to encapsulate functional biodegradable polymer films for substrate mediated gene delivery. 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 SuperFectTM consisting of activated dendrimers is commercially available.

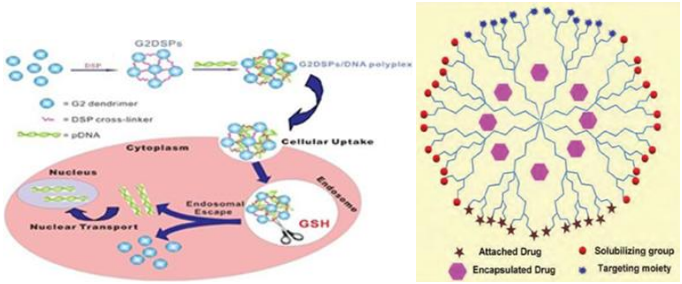

Fig. 21 Gene delivery by dendrimer

d) For nanoparticles encapsulation

Dendrimers are also used in the synthesis of mono disperse metallic nanoparticles. Poly(amidoamide), or PAMAM, dendrimers are utilized for their tertiary amine groups at the branching points within the dendrimer. Metal ions are introduced to an aqueous dendrimer solution and the metal ions form a complex with the lone pair of electrons present at the tertiary amines. After complexion, the ions are reduced to their zerovalent states to form a nanoparticle that is encapsulated within the dendrimer.

e) In Sensor Technology

Scientists have also studied dendrimers for use in sensor technologies. Studied systems include proton or pH sensors using cadmium- sulfide- polypropylenimine tetrahexaconta amine dendrimer composites to detect fluorescence signal quenching, and poly(propylenamine) first and second

generation dendrimers for metal cation photo detection amongst others. Research in this field is vast and ongoing due to the potential for multiple detection and binding sites in dendritic structures[94].

f) Blood Substitution

Dendrimers are also being investigated for use as blood substitutes. Their steric bulk surrounding a heme-mimetic centre significantly slows degradation compared to free heme and prevents the cytotoxicity exhibited by free heme.[95, 96]

g) As Drug Carriers in Sexually Transmitted Diseases

Dendrimers as Nano-Drug carriers are useful against the herpes simplex virus as it can potentially prevent or reduce transmission of HIV and other sexually transmitted diseases (STDs), when drug delivery is made through Poly(lysine) dendrimers modified with sulfonated naphthyl groups.[97]

h) Dendrimer in Ocular Drug Delivery

PAMAM dendrimers with carboxylic or hydroxyl surface groups, have been reported in improving residence time and enhancing bioavailability of pilocarpine in the eye.[98]

i) Dendrimers in Pulmonary Drug Delivery

Positively charged PAMAM dendrimers (G2 and G3 generation) increased the relative bioavailability of pulmonary drug delivery of Enoxaparin.[99]

j) Dendrimer in transdermal drug delivery

Dendrimers has been found improve solubility and plasma circulation time via transdermal and to deliver drugs efficiently. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) have been reported to improve the drug permeation through the as penetration enhancers. Ketoprofen and Diflunisal were with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. Enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application was to be effective.

k) Dendrimer in oral drug delivery

Oral drug delivery studies the colon adenocarcinoma cell line, Caco2, have indicated that low generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the P-glycoprotein efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively.

l) Dendrimer hydrogel for ocular drug delivery

Dendrimers are especially ideal for synthesizing hydrogels, cross-linked networks that increase in volume in aqueous solution and are more similar to living tissue than any other synthetic compound. By adding polyethylene glycol or PEG groups to the dendrimers, these hydrogels have applications including cartilage tissue production and for sealing ophthalmic injuries. By synthesizing a hydrogel composed of PEGylated dendrimers that contain ocular drug molecules attached to the dendrimers efficiently deliver the drugs to the eye.

m) Cellular Delivery Using Dendrimer Carriers

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.

5. Dendrimer as Solubility Enhancers

There are many substances, which have a strong therapeutic activity but due to their lack of solubility in pharmaceutically acceptable solvents have not been used for therapeutic purposes. Water soluble dendrimers are capable of binding and solubilizing small acidic hydrophobic molecules with antifungal or antibacterial properties. Dendrimers having a hydrophobic core and a hydrophilic surface layer, have been termed unimolecular micelles. A hydrophilic–hydrophobic core-shell dendrimer with PAMAM interior and long alkane chain exterior was shown to bind 5-flurouracil, a water-soluble anti-tumor drug. Dendrimers have unimolecular miceller nature, due to hydrophilic exterior and hydrophobic interiors it forms covalent as well as non covalent complexes with drug molecules and hydrophobes and enhance its solubility behaviour.

6. 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. Photosensitive 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.

7. 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 can potentially prevent/reduce transmission of HIV and other sexually transmitted diseases (STDs). Chitosan– dendrimer hybrids have been found to be useful as antibacterial agents, carriers in drug delivery systems, and in other biomedical applications

C. Miscellaneous Applications of The Dendrimers

- Delivery of nucleic acids.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.

Dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands targeting components, radio ligands, imaging agents, or pharmaceutically active compounds.

D. Current and Potential Applications of Dendrimers:

- Delivery of Nucleic acids, Encapsulated drugs and Covalently linked drugs.
- Film-forming agents for controlled release.
- Lubricants for pharmaceutical processing and engineering.
- New carrier system for drug delivery (gels, self-associating systems)
- Vaccines against bacteria, viruses and parasites.
- Modification of cell-cell interactions and gene expression (e.g.: alteration of transcription factors binding to DNA)
- Diagnostic reagents in: serodiagnosis (systems with surface ligands), Biosensor systems (systems containing dyes, reactive molecules) magnetic resonance imaging (e.g.: gadolinium adducts).
- Dendrimers typically involve conjugating other chemical species to the dendrimer surface that can function as detecting agents (such as a dye molecule), affinity ligands, targeting components, radio ligands, imaging agents, or pharmaceutically active compounds

Today, dendrimers have many medicinal and practical applications. Firstly, they are used in cardiac testing. In this method, proteins from a blood sample are attached to glass by dendrimers. The result tells if there is any muscle damage, and significantly reduces the testing time from 40 minutes to 8. Dendrimers are also used as contrast agents in MRIs (Magnetic resonance imaging). Contrast agents improve sensitivity and specificity during the imaging process. One dendrimer molecule has hundreds of possible sites to couple to an active species. This might allow researchers to attach both targeting molecules and drug molecules to the same dendrimer, which could reduce negative side effects of medications on healthy cells.

CYTOTOXICITY ISSUES REPORTED IN VIVO

a. Dendrimers with positively charged surface groups prone to destabilize cell membranes and cause cell lysis.
b. Generation dependent toxicity-higher generation dendrimers being the most toxic.
c. Degree of substitution, type of amine functionality is important- primary amines being more toxic than secondary or tertiary amines

- **Toxicity and Pegylation:-**

It is known that the dendrimers may have toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity. Therefore, PAMAM dendrimers are more cationic than anionic cytotoxic. An example of interaction with lipid bilayers of cells occurs with the cationic dendrimer-G7 PAMAM which comes to form holes 15-40 nm in diameter, which disturbs the flow of electrolyte causing cell death. Many toxic effects of dendrimers are attenuated at their surfaces with hydrophilic molecules and poly (ethylene glycol) (PEG) which masks the surface charge cationic dendrimers improving biocompatibility and increasing the solubility of the polymers. The pegylated dendrimers have lower cytotoxicity and longer stay in the blood than non-pegylated dendrimers. PEGylation increases the physical dendrimers size which reduces renal clearance.

Limitations of dendrimers

- An intact dendrimer-drug construct does not generally cross the gut wall and so the approach may not be a good choice for certain oral administration applications. Obviously this

limitation does not apply where the drug is solublised with dendrimer and then released in the gut for absorption.

- The drug-dendrimer construct will generally be considered to be a New Chemical Entity (NCE), meaning that clinical testing of the new construct may be required. This is normally not seen as an issue for preclinical drugs, which will require full clinical testing anyway, but the approach may require review before application to a candidate already in the clinic. Helpfully, the construct may be considered to be a prodrug allowing bridging data from previous studies to be used.

MARKETED PRODUCTS AVAILABLE

Table. 4 Marketed products of dendrimers

Product	Company	Utilization
Starburst	Dow chemical	Targeted diagnostic and therapeutic delivery
Priostar	Starpharma	For cancer.
Stratus CS	Dade Behring	Cardiac marker
Vivagel	Starpharma	Vaginal Gel for Prevention of HIV infection
Alert ticket	US Army Research Lab.	Anthrax detection
SuperFect	Qiagen	Gene transfection
Taxotere	Sanofi Aventis	Anticancer drug delivery[100]

CONCLUSION

Dendrimer drug delivery is in its infancy, it offers several attractive features. This novel class of polymers and their derivatives exhibit unique physicochemical and biological properties, which have great potential for use in variety of applications. It has greater flexibility in design.High control over branching length ,shape and size allows modification according to delivery system, so these serves as ideal carrier for drug and other application. The main purpose of this review is to focus various valuable applications of dendrimer . We still do not know whether these synthetic polymer, once they entered the body can cause damage to other tissue. Even though toxicity problem if arise, that will be minimized by modifying dendrimer architecture. As the system involves multistep process future work is necessary to find out cost effective synthesis strategies.

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