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Review Article

DENDRIMERS- AN EXCELLENT POLYMER FOR DRUG DELIVERY SYSTEM

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ABSTRACT

Dendrimers is a type of synthetic polymer. Dendrimer is a novel polymer for various drug delivery systems. A dendrimer is described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Dendrimers are monodisperse supramolecule having hyperbranched architecture. As the dendrimers have these properties so it is suitable carrier for drug delivery system. Dendrimers are unimolecular micceller in nature and due to this enhances the solubility of poorly soluble drugs. It has main components i.e. core, branches and end groups. It is also called as cascade molecule. It achieves the controlled and targeted release of drug restricted to the desired area. It has main property of polyvalency i.e presence of many active groups for targeting drug to delivery site. During process of synthesis, properties of dendrimers such as its molecular mass, size, surface group can be controlled and constructed to the desired need. Under this topic we have included what is dendrimer, advantages, properties, factors affecting properties of dendrimers, structure of dendrimers, types of dendrimers, synthesis, characterization of dendrimers. It has various applications for oral, ocular, transdermal, nanodrugs, pulmonary, controlled and targeted drug delivery systems.

Keywords: *- Dendrimers, PAMAM dendrimers, properties, divergent,convergent.*

INTRODUCTION

Dendrimer is a nanoparticle (10^{-9}) and so has advantages over microparticles or others due to its small size, easy uptake by cells [3]. Dendrimer word come from the Greek word i.e. “Dendron” means tree and “Meros” means part. The another name for dendrimers are arborols and cascade molecules [1].

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In 1978, the first dendrimers were made by divergent synthesis by Fritz Vogtle [2]. There are three basic components of dendrimers i.e. core, branches and end groups (surface ligand). There are various types of dendrimers and it is used as a polymeric material. There are two synthesis process for dendrimers viz. divergent and convergent synthesis.

Definition of dendrimers

Dendrimers are hyper-branched, globular, monodisperse, three dimensional synthetic polymers, having very well defined size, shape and definite molecular weight (1).

Difference between dendrimers and dendrons

A dendrimer is typically symmetric around the core, and often adopts a spherical three-dimensional morphology. A dendron usually contains a single chemically addressable group called the focal point [2].

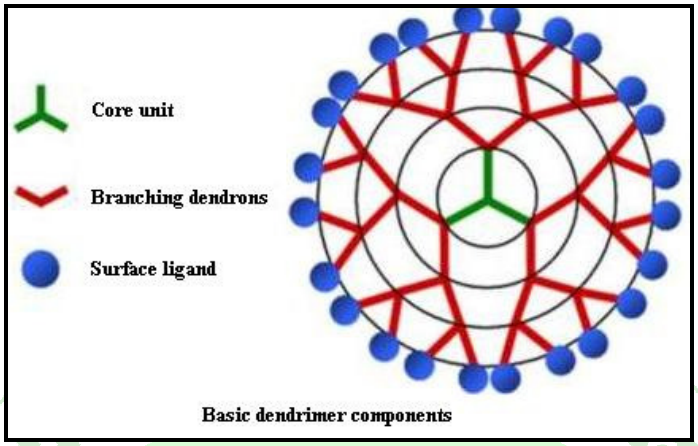


Fig. 1:- Basic components of dendrimers

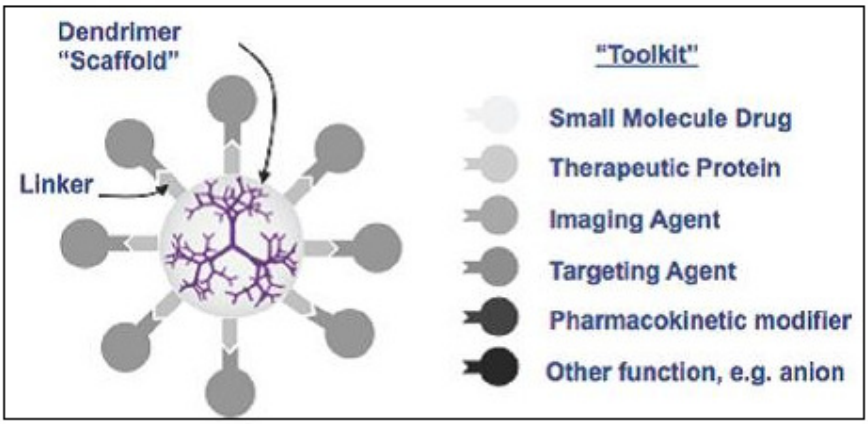


Fig.2:- Structure of dendrimers

OBJECTIVE:-

- Improve the pharmacokinetic and pharmacodynamic properties of a drug so that there is also an increase in bioavailability.
- Achieve the controlled and targeted release of drug restricted to the desired area.

ADVANTAGES OF DENDRIMERS OVER OTHER POLYMERS:

- Dendrimers have nanoscopic particle size range from 1 to 100 nm, which makes them less susceptible for reticuloendothelial system (RES) uptake.
- 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.
- Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body.
- Dendrimers might show an enhanced permeability and retention effect (depending on their molecular weight) that allows them to target tumor cells more effectively than small molecules.
- 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 [4].

PROPERTIES: [2]

- Dendritic molecules are characterized by structural perfection.
- Dendrimers and dendrons are monodisperse and usually highly symmetric, spherical compounds.
- The field of dendritic molecules can be roughly divided into low molecular weight and high-molecular weight species. The first category includes dendrimers and dendrons, and the latter includes dendronized polymers, hyperbranched polymers, and the polymer brush.
- The properties of dendrimers are dominated by the functional groups the molecular surface. Dendritic encapsulation of functional molecules allows for the isolation of the active site, a structure that mimics that of active sites in biomaterials. Also, it is possible to make dendrimers water soluble, unlike most polymers, by functionalizing their outer shell with charged species or other hydrophilic groups.
- Other controllable properties of dendrimers include toxicity, crystallinity, tecto-dendrimer formation, and chirality.
- One important property of dendrimers is "polyvalency" or the presence of multiple active groups on the surface of the dendrimer. This is significant because simultaneous presentation of active groups can yield entirely new or enhanced activity compared to single presentation of the same active group.

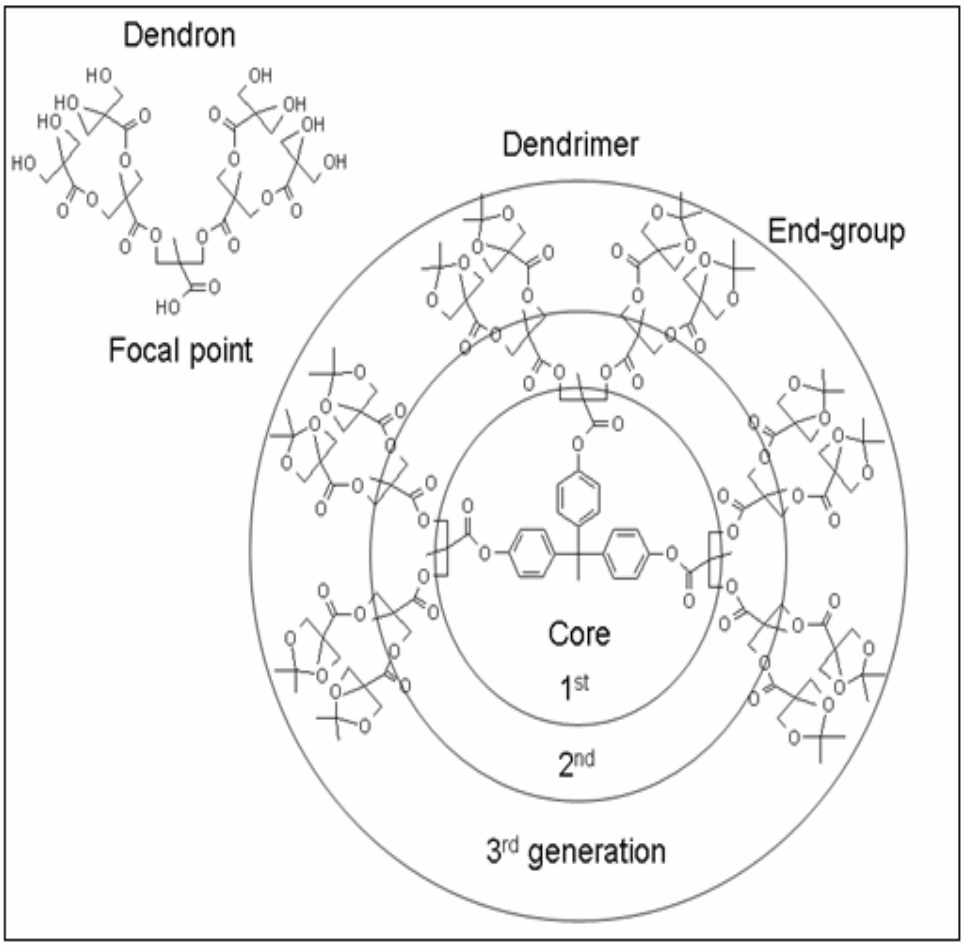


Fig. 3:- Difference between dendrimers and dendrons

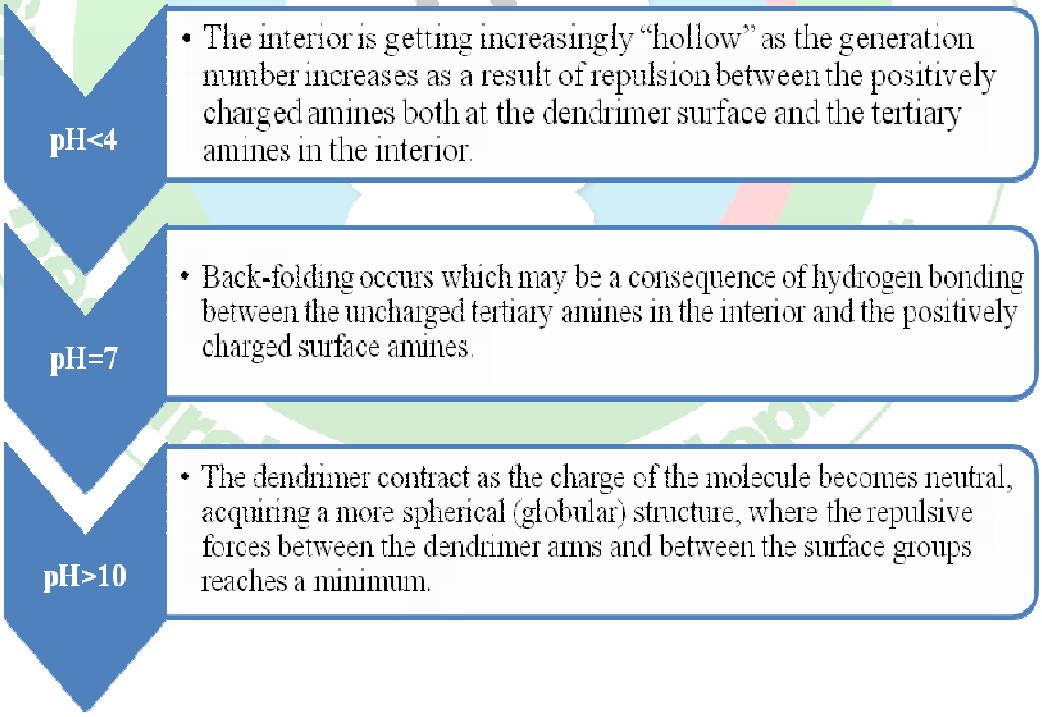
TABLE 1:- PROPERTIES OF DENDRIMERS

Property	***Dendrimers***
Structure	Compact, globular
Synthesis	Careful and stepwise growth
Structural control	Very high
Architecture	Regular
Shape	Spherical
Crystallinity	Amorphous material- lower glass temperature
Polar solubility	High
Non-polar solubility	High
Reactivity	High
Compressibility	Low
Polydispersity	Monodisperse

FACTORS AFFECTING PROPERTIES OF DENDRIMERS:-[5]

pH effect:-

Amino-terminated PPI and PAMAM dendrimers have basic surface groups as well as a basic interior. Applying molecular dynamics to predict the structural behaviour of PAMAM dendrimers as a function of pH shown as follows:-



Solvent effect:-

The ability of the solvent to solvate the dendrimer structure is a very important parameter when investigating the conformational state of a dendrimer. Dendrimers of all generations generally experience a larger extent of back-folding with decreasing solvent quality, i.e. decreasing solvation.

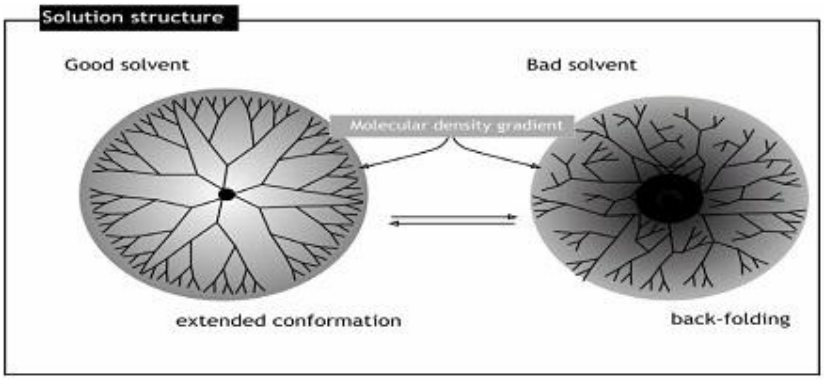
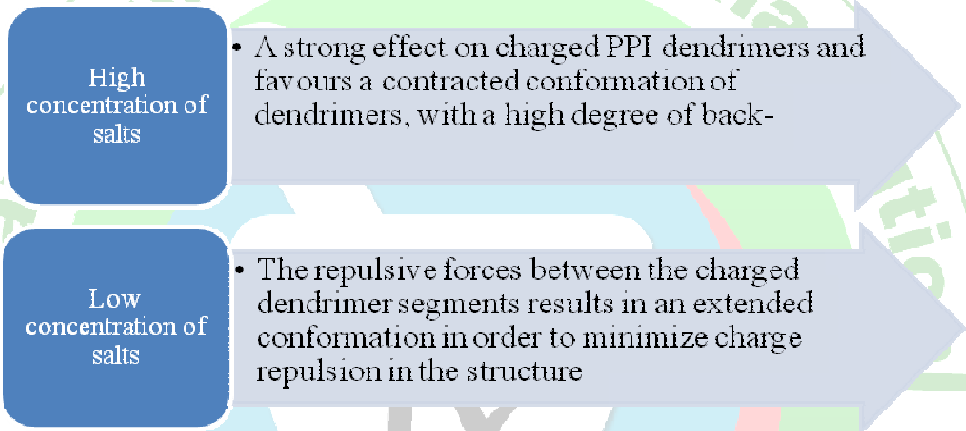


Fig. 4:- Effect of solvent

Salt effect:-



Concentration effect:-

PPI dendrimers in a polar solvent: The molecular conformation of dendrimers upon increasing concentration becomes increasingly contracted.

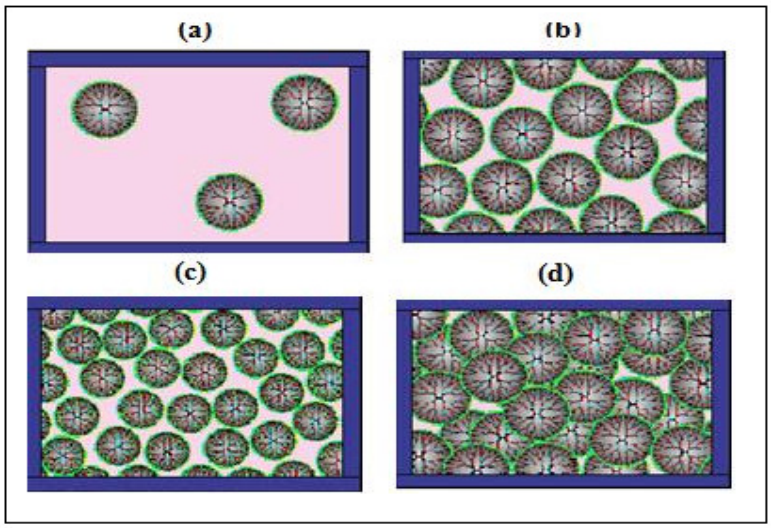


Fig.5: Dendrimer at different concentrations (a) Dilute (b) Contact (c) Collapse (d)Interpenetrate

STRUCTURE OF DENDRIMERS

A dendrimer is typically symmetric around the core, and has three dimensional morphology. In the view of polymer chemistry dendrimers are perfect monodisperse macro molecules with regular highly branched three dimensional structures and consist of three architectural components like core, branches and end groups.

Generation:-

Dendrimers of lower generations (0, 1, and 2) have highly asymmetric shape and possess more open structures as compared to higher generation dendrimers. As the chains growing from the core molecule become longer and more branched (in 4 and higher generations) dendrimers adopt a globular structure. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane-like structure. When a critical branched state is reached dendrimers cannot grow because of a lack of space. This is called the 'starburst effect'**[10]**. For PAMAM dendrimer synthesis it is observed after tenth generation. The tenth generation PAMAM contains 6141 monomer units. The increasing branch density with generation is also believed to have striking effects on the structure of dendrimers. They are characterized by the presence of internal cavities and by a large number of reactive end groups. Dendritic copolymers are a specific group of dendrimers. There are two different types of copolymer:-

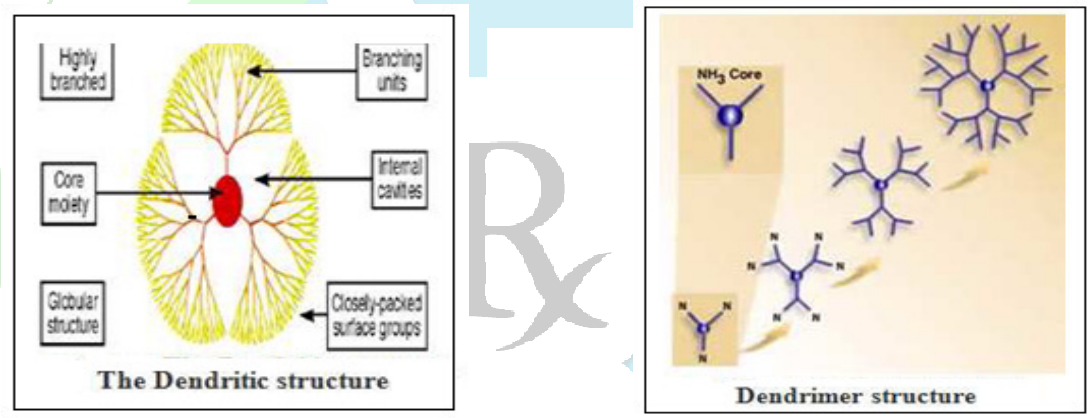


Fig. 6:- Structure of Dendrimers

Segment-block dendrimers are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one polyfunctional core molecule.
Layer-block dendrimers consist of concentric spheres of differing chemistry.They are the result of placing concentric layers around the central core.

Shell

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

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".

TYPES OF DENDRIMERS

- PAMAM Dendrimers
- PPI Dendrimers
- Chiral Dendrimers
- Multilingual Dendrimers
- Tecto Dendrimers
- Hybrid Dendrimers
- Amphiphilic Dendrimers

- Frechet-Type Dendrimers
- Peptide Dendrimers
- PAMAMOS Dendrimers(1)

PAMAM Dendrimers [Poly (Amido Amine)]:

Pamam [Poly (amido amine)] dendrimers are spheroidal or ellipsoidal in shape.
Ammonia or ethylenediamine is used as a starting material for synthesis of PAMAM dendrimers by divergent method.

Due to presence of a number of functional end groups and empty internal cavities, it has high solubility and reactivity [1]

PPI /POPAM Dendrimers:

Synonyms :- PPI means Poly (Propylene /Imine)/ Poly (Propylene Amine)
Core structure- diamino butane
End groups- primary amines
Interior - tertiary -propylene amines
These are commercially available up to G-5. [1]

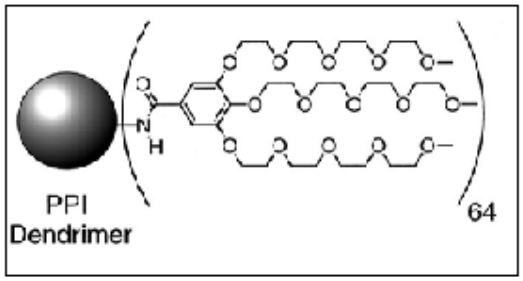


Fig .7:- PPI /POPAM Dendrimers

Chiral Dendrimers:

The chirality of the dendrimers are based upon the construction of constitutionally but chemically similar branches to chiral core. [1]

Multilingual Dendrimers:

It contains multiple copies of a particular functional group on their surface. [1]

Tecto Dendrimers:
These are made up of core dendrimers which is surrounded by other dendrimers, each one of which perform a specific function leading to a smart therapeutic system which can simultaneously diagnose the diseased state and deliver API to the recognized diseased cell. [1]

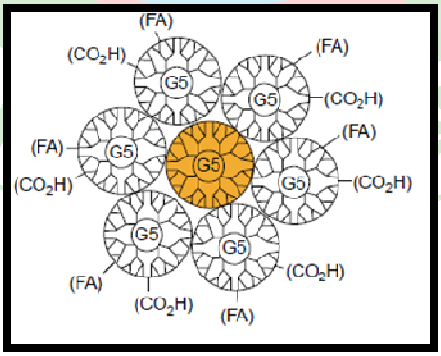


Fig. 8: Tecto Dendrimers

Hybrid Dendrimers: These dendrimers have characters of both dendritic and linear polymer. [1]

Amphiphilic Dendrimers: It has one half that is electron donating and another half is electron withdrawing. [1]

Peptide Dendrimers: It contains amino acid as branching or interior unit. These are used for diagnostic purpose and vaccine delivery. [1]

Frechet-Type Dendrimers: These are based on polybenzyl ether hyper branched skeleton. Carboxylic acid group found upon the surface of dendrimers which provides site for further functionalization and also enhance the solubility of dendrimers. [1]

PAMAMOS Dendrimers [Poly (Amidoamine- Organosilicon)]
These are inverted unimolecular micelles that contain exterior hydrophobic organosilicon(OS) and interiorly hydrophilic, nucleophilic polyamidoamine. [1]

SYNTHESIS OF DENDRIMERS:-
There are four methods but first two are important:-

- Divergent growth method
- Convergent growth method
- Double Exponential' growth
- Hypercores' and 'Branched Monomers' growth

Divergent Method:

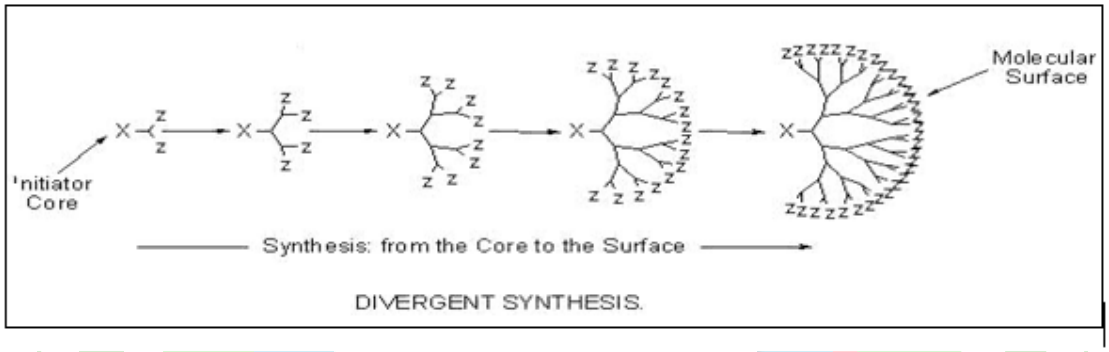


Fig. 9:- Divergent Method

The dendrimer is consist of a multifunctional core, which is extended outward by a series of reactions, commonly a Michael reaction. In this method the dendrimers grow from inside (i.e. core molecule) to outside. In this the reactive core molecule reacts with the monomer molecule, which has two dormant and one reactive group. This combination gives 1st generation dendrimers. The 1st generation dendrimers have the reactive periphery, which reacts with other monomer molecule and gives the 2nd generation dendrimers. This process is continued for several generations. Each step of the reaction must be driven to full completion to prevent mistakes in the dendrimer, which result in trailing generations (some branches are shorter than the others). Such impurities can affect the functionality and symmetry of the dendrimer, but are extremely difficult to purify out because the relative size difference between perfect and imperfect dendrimers is very small.[2] PAMAM is the 1st synthesized dendrimers by using divergent growth method. Main problem with the divergent method is the side reactions and incomplete reactions of the end group. For prevention of this problem a large quantity of reagent is required [1].

Convergent Method:

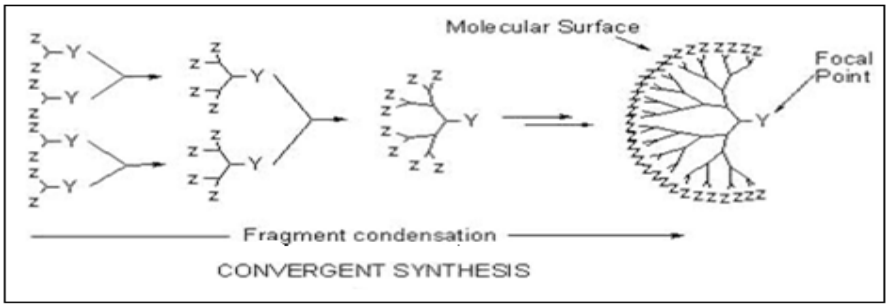


Fig. 10:- Convergent Method

In this method the dendrimers grow from outside to inward It is a two step synthesis.

1st Step: The surface units' links together to form a large wedge.

2nd Step: The large surface units attached to the multifunctional core units.

Advantages:
Product is easily purified.
Minimization of defect in the final structure, so that the final dendrimer is more monodisperse.

Limitation:
High generation dendrimers cannot be formed by this method because of steric hindrance effect [1].

Double Exponential and Mixed Method:

It is most advance and recent method of dendrimers synthesis. This is a mixture of both divergent and convergent method. In this method a single starting material is taken from which two monomers are prepared by divergent and convergent method. Then these two monomers are reacted together to give an orthogonally protected trimer [1].

Hypercores' and 'Branched Monomers' growth

Linkage of the oligomeric species in a radial, branch-upon-branch. Core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation dendrimers [3].

CHARACTERIZATION OF DENDRIMER

Following methods can be used for characterization of dendrimer:-

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

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

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

Size exclusion chromatography (SEC)

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

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

Miscellaneous like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc. [5]

APPLICATIONS OF DENDRIMERS IN DRUG DELIVERY: [3]

Various routes for dendrimer drug delivery:

Oral, Parenteral, Intra-ocular, Nasal

Gene therapy, immunodiagnostics:

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.

Dendrimer in ocular drug delivery

To enhance pilocarpine bioavailability.

Dendrimers in pulmonary drug delivery

For Enoxaparin (40% increase in relative bioavailability by G2 and G3 generation positively charged PAMAM dendrimers).

Dendrimer in transdermal drug delivery

Improvement in solubility and plasma circulation time. PAMAM dendrimer complex with NSAIDs as permeation enhancers.

Dendrimers for controlled release drug delivery

Anticancer drugs like methotrexate, adriamycin. Some of the methods to initiate the release include light, removal of protecting groups, and antibodies. 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).

Dendrimers in targeted drug delivery

Folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains.

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).

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. Photos ensitive 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.

Table 2:- Dendrimers used for various drug formulation

DRUG	*DENDRIMERS USED*
Ketoconazole	**PAMAM [6]**
Chloroquine phosphate	**PEGylated-poly-l-lysine [7]**
Ketoprofen and Diflunisal	**PAMAM**
Flurouracil	**PEGylated PAMAM**
Folate	**PEGylated PAMAM**
Piroxicam	**PAMAM**
Lamivudine	**Mannosylated poly (propyleneimine) dendrimer**
Doxorubicin	**PAMAM**
Simvastatin	**PAMAM**
Ketoprofen	**Polyamidoamine dendrimers**

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