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Pharmaceutical Sciences **Review Article……!!!**

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DENDRIMER: A NANOCARRIER

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ABSTRACT

The object of the review is mainly on the architecture, synthesis, properties and applications of the Dendrimers. Dendrimers are macromolecules of highly symmetrical, hyper-branched and globular structure. Dendrimers are rapidly expanding area. These are nanoparticle based drug delivery system. They have numerous applications in pharmacy such as gene transfection, oligonucleotides and DNA delivery, tumour therapy, targeting drug at specific site, enhance the solubility of the poorly soluble drugs, ability to act as carriers for the development of drug delivery system etc. They are very small size, monodispersity, stability make it an appropriate carrier for delivering drugs with precision and selectivity. There is reduction in amount of drug and systemic toxicity while the therapeutic efficacy increases. Thus the present review focuses on the fundamentals of Dendrimers and their use as drug delivery agents in treatment of disorders.

INTRODUCTION

Drug delivery is an important aspect of formulation as it is a proper choice that enhances the bioavailability, enhances the solubility, targets the action and reduces the toxicity.One of the main approach which focuses on the above criteria is Dendrimers[1]. The word “dendrimer” originated from two words, the Greek word “dendron”, meaning tree, and “meros”, meaning part. Dendrimers are different from traditional polymers in that they have a multi-branched, threedimensional architecture with very low polydispersity and high functionality**.** Dendrimer is a nanoparticle(10^{-9}) based drug delivery system, which are macromolecules of highly symmetrical, hyper-branched (Fig 2), globular structure and monodisperse structure consisting of tree-like arms or branches[2,3]**.**They have an architecture of

i. Core-determines the size and shape of the dendrimer
ii. An interior of shells-determines amount of void space that can be enclosed by dendrimer
iii. An exterior layer-allows growth of the dendrimer(or)other chemical modification (Fig 1)

This unique structure makes Dendrimers monodispersed macromolecules compared to classical linear polymers. In dendritic structures number of terminal group increases exponentially with a linear increase in the generation of dendrimer. This relationship limits the ultimate size of the dendrimer due to steric crowding of the terminal groups[8]. Several new branching points are available at each repeating unit in their structure for hyperbranched growth. The manufacturing process is a series of repetitive steps generating shells, starting with a central initiator core. Each subsequent shell represents a new "generation" of polymer with a larger molecular diameter, twice the number of reactive surface sites and approximately double the molecular weight of the preceding generation[12].

Objectives:

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

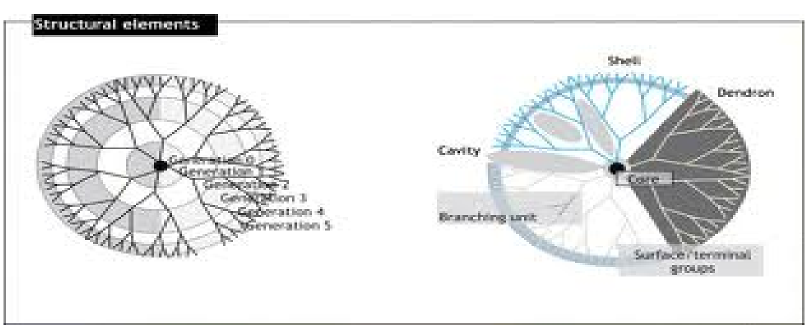


Figure 1: Structure of dendrimer

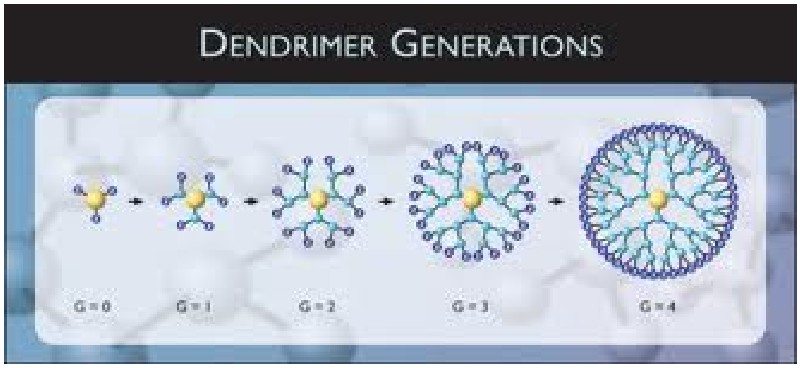


Figure 2: Generation of dendrimer

STRUCTURE OF DENDRIMERS

A dendrimer is typically symmetric around the core (figure 1), and often develops a three dimensional morphology .In the view of polymer chemistry dendrimers are perfect monodisperse macro molecules with regular highly branched three dimensional structures (figure 2) and consist of three architectural components like core, branches and end groups.[4,5] 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[6]**.**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’’[7]. For PAMAM dendrimer synthesis it is observed after tenth generation. The rate of reaction drops suddenly and further reactions of the end groups cannot occur. The tenth generation PAMAM contains 6141 monomer units and has a diameter of about 124 Å [8].The increasing branch density with generation is also believed to have striking effects on the structure of dendrimers. They are characterised by the presence of internal cavities and by a large number of reactive end groups (Figure 3). Dendriticcopolymers are a specific group of dendrimers. There are two different types of copolymer.

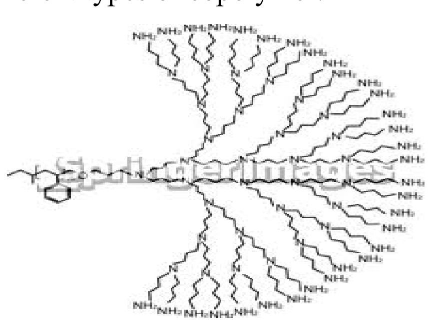


Figure3

Segment-block Dendrimers are built with dendritic segments of different constitution. They are obtained by attaching different wedges to one polyfunctional core molecule[9].

Layer-block Dendrimersconsist of concentric spheres of differing chemistry.

They are the result of placing concentric layers around the central core. Hawker and Fréchetsynthesised a segment- block dendrimer which had one ether-linked segment and two ester-linked segments[10].

They also synthesised a layer-block dendrimer. The inner two generations were ester-linked and the outer three etherlinked. The multi-step synthesis of large quantities of higher generation Dendrimers requires a great effort. This was the reason why Zimmerman's group applied the concept of self-assembly to dendrimer synthesis[11].

They prepared a wedge like molecule with adendritic tail in such a manner that six wedge-shaped subunits could self-assemble to form a cylindrical aggregate. This hexameric aggregate is about 9 nm in diameter and 2 nm thick. It has a large cavity in the centre. The six wedges are held together by hydrogen bonds between carboxylic acid groups and stabilised by Vander Waals interactions. However, the stability of the hexamer is affected by many factors. The aggregate starts to break up into monomers when the solution is diluted, when the aggregate is placed in a polar solvent like tetrahydrofuran (THF), and when the temperature is high. The hexamer's limited stability is due to its noncovalent nature.

SYNTHESIS OF DENDRIMER

- Divergent growth method
- Convergent growth method
- Hyper cores and branched monomers growth
- Double exponential growth

First two are the Main two methods for synthesis of dendrimers.

(a) Divergent growth method [figure a] This method was introduced by Tomalia. In this method growth of Dendrimers originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups, lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained. By this approach the first synthesized Dendrimers were polyamidoamines (PAMAM), also known as starbust Dendrimers[12].

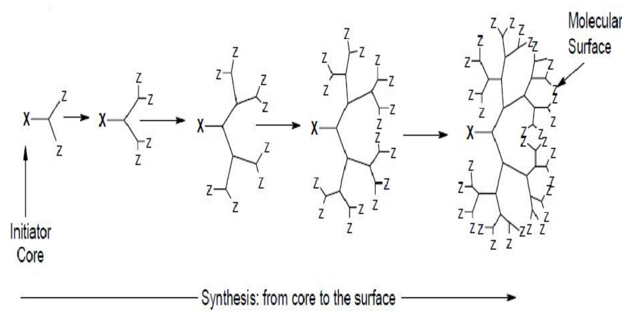


Figure (a) divergent synthesis of dendrimer

(b) Convergent Dendrimer Growth [Figure b]

Convergent dendrimer growth begins at what will end up being the surface of the dendrimer, and works inwards by gradually linking surface units together with more. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. convergent growth method has several advantages like relatively easy to purify the desired product, occurrence of defects in the final structure is minimised, does not allow the formation of high generation dendrimer because stearic problems occur in the reactions of the dendrons and the core molecule[13].

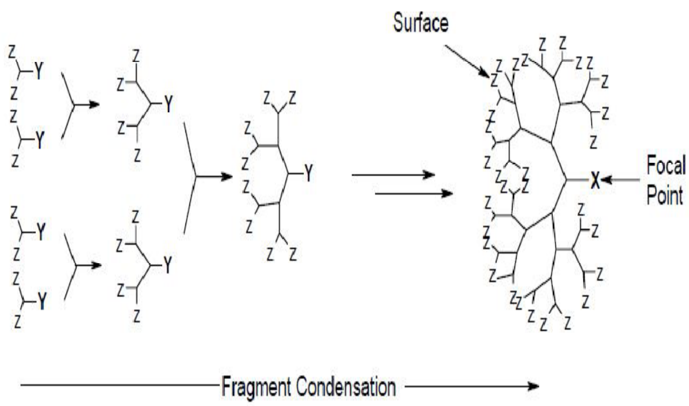


Figure (b) convergent synthesis of dendrimer

An advantage of convergent growth over divergent growth is that purification Is done after each step whereas in divergent method since the reactant and product remains same it is difficult to purify by chromatographic technique[14,15.]

(c) Hypercores' and 'Branched Monomers' growth(Figure 4)- 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[16.]

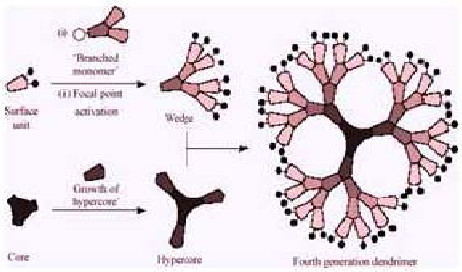


Fig.4. 'Hypercores' and 'Branched Monomers growth

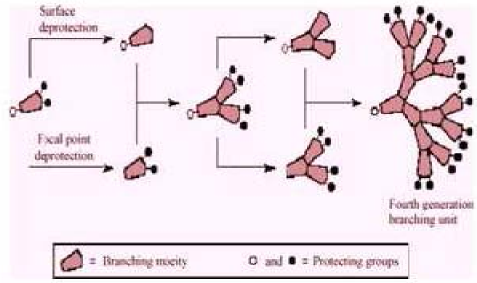


Fig 5. 'Double Exponential' growth

(d) Double Exponential' or mixed growth(Fig 5)-

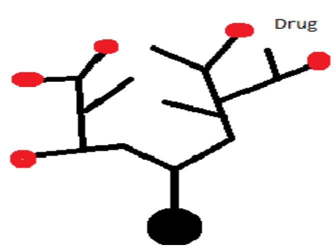
In this approach two products (monomers for both convergent and divergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps[17,18].

MECHANISM OF DRUG DELIVERY THROUGH DENDRIMERS:

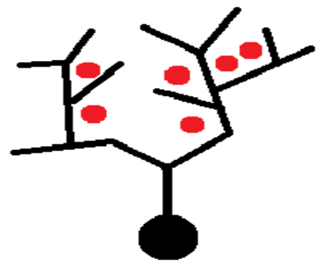
The well defined 3D structure and many functional surface groups, drug molecules can be loaded both in the interior of the Dendrimers as well as attached to the surface groups (as shown in the figure). Dendrimers can function as drug carriers either by encapsulating drugs within the dendritic structure, or by inter-acting with drugs at their terminal functional groups via electrostatic or covalent bonds (prodrug) [17,19,20].

There are broadly two mechanisms for drug delivery.

i. Drug molecules can be physically entrapped within the dendritic structure 1.1
ii. Drug molecules can be covalently linked onto the dendrimer surface (or) other functionalities to produce dendrimer-drug conjugate 1.2



A Dendrimer molecule with drug molecules Loaded at terminal surface of branches Figure1.2



Dendrimer molecules with drug molecules Encapsulated within branches Figure1.1

FUNCTIONAL COMPONENT

A dendrimer of higher generations consists of shell. A shell consists of a central core and alternating two layers of monomers around it. Amines constitute the central core which may sometimes be replaced by sugar. All core molecules have multiple and identical reaction site. Amine is the simplest core molecule present with three functional sites. The surface of all full generations consists of multiple amines, while the surface of the half generations consists of multiple acids. These two kinds of surfaces provide the means of attachment of multiple different functional components [21.]

PROPERTIES OF DENDRIMER: [22]

Table 1: Properties of Dendrimer and linear polymers

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

TYPES OF DENDRIMER

(1)Radially layered poly (amidoamineorganosilicon) Dendrimers(PAMAMOS)

In 1990, Dr.PetarDvornic and his colleagues at Michigan Molecular Institute discovered this unique first commercial silicon containing dendrimers. Consist of hydrophilic, nucleophilicpolyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. Excellent its networks regularity and ability to complex and encapsulate various guest species offer unprecedented potentials for new applications in nanolithography, electronics, photonics, chemical catalysis etc. and useful precursors for the preparation of honeycomb like networks with nanoscopic PAMAM and OS domains[23,24.]

(2) Poly (amidoamine) dendrimers(PAMAM)

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylenediamine. When looking at the structure of the high generation in two-dimensions, star like pattern observed. They are commercially available as methanol solutions and ingeneration G 0-10 with 5 different core type and 10 functional surface groups[25,26.]

(3) Poly (Propylene Imine) dendrimers(PPI)

Poly (Propylene Imine) dendrimers (PPI) generally having poly-alkyl amines as end groups, and numerous tertiary trispropylene amines present in interior portion. It commercially available up to G5, and wide applications in material science as well as in biology [27.]PPIdendrimers are available as Astramol™.

(4) Chiral dendrimers

The chirality in these dendrimersis based upon the construction of constitutionally different but chemically similar branches to chiral core. Their potential use as chiral hosts for enantiomeric resolutions and aschiral catalysts for asymmetric synthesis.

(5) Liquid crystalline dendrimers

A highly-branched oligomer or polymer of dendritic structure containing mesogenicgroups that can display mesophase behaviour. They consist of mesogenic (liq. crystalline) monomers e.g. mesogenfunctionalizedcarbosilanedendrimers.

(6) Tecto dendrimer

Tecto Dendrimer are composed of a core dendrimer, perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

(7) Hybrid dendrimers

Hybrid dendrimers are hybrids (block or graft polymers) of dendritic and linear polymers. Obtained by complete monofunctionalization of the peripheral amines of a "zero-generation" polyethyleneimine dendrimer, provide structurally diverse lamellar, columnar, and cubic self organized lattices that are less readily available from other modified dendritic structures.

(8) Multilingual Dendrimers

Multilingual Dendrimers contains multiple copies of a particular functional group on the surface.

(9) Micellar Dendrimers

Micellar dendrimers are unimolecular water soluble hyper branched polyphenylenes micelles.

CHARACTERIZATIONS OF DENDRIMER BY VARIOUS METHODS [16]

S. NO	Techniques	Applications
1	**Spectroscopy techniques** **A.NMR.** Special techniques of NMR 1H and 13 NMR Two dimensional: 1H, 1H COSY 1H,1H NOESY 1H,1H EXSY 1H,1H TOCSY	Most widely used for dendrimers characterization. Analysis in step by step synthesis Of Dendrimer .To Probe The Size ,Morphology, Dynamics of Dendrimers for organic dendrimers such ad PPI, polyphenylester. For polyphenyacetylene or polyaryldendrimers For PPI dendrimers For polyamide dendrimers For melamine dendrimers
2	**UV-Vis method.**	Used to monitor synthesis of dendrimers. The intensity of the absorption band is essentially proportional to the number of chromophoric units.
3	**Infra red spectroscopy**	For routine analysis of the chemical transformations Occurring at the surface of dendrimers.

4	**Near Infra red spectroscopy**	Used to characterized delocalize π-π stacking interaction between end group of modified PANAM.
5	**Fluorescence**	The high sensitivity of fluorescence has been used toquantify defects during the synthesis of dendrimers
6	**Mass spectroscopy**	Chemical ionization or fast atom bombardment can beused only for the characterization of small Dendrimers whose mass is below 3000 Da. Electrospray ionization can be used for Dendrimers able to form stable multicharged species.
7	**X-ray diffraction**	This technique should allow precise determination of the chemical composition ,structure, size and shape of dendrimer
8	**Microscopy** **Transmission microscopy**	Electron or light produce images that amplify the original, with a resolution ultimately limited by thewavelength of the source.
9	**Scanning microscopy**	The image is produced by touch contact Q at a few angstroms of a sensitive cantilever arm with sample. Ex. Atomic force microscopy.
10	**chromatography**	Size exclusive or gel permeation chromatography allows the separation of molecules according to size.
11	**Electrical techniques** **A. Electron paramagnetic resonance** **B.Electrochemistry**	Quantitative determination of the substitution Efficiency on the surface of PANAM dendrimers. It give information about the possibility of interaction of electro active end groups
12	**electrophoresis**	Used for assessment of purify and homogeneity of several type of water soluble dendrimers.

13	**Rheology, Physical properties A. Intrinsic viscosity**	Used as analytical probe of the morphological structure of dendrimers.
14	**Differential scanning calorimetry**	Used to detect the glass transition temperature which depends on thy molecular weight, entanglement andchain composition of polymers.
15	**Dielectric spectroscopy**	Gives information about molecular dynamic processes

APPLICATIONS OF DENDRIMERS

1) **Various routes for dendrimer drug delivery:** oral, parenteral, intra-ocular, nasal, transdermal etc.

2) **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 cellnucleus[28.]

3) **Dendrimer in ocular drug delivery-** to enhance pilocarpine bioavailability using PAMAM Dendrimers with carboxylic and hydroxyl groups.

4) **Dendrimers in pulmonary drug delivery- for** Enoxaparin (40% increase in relative bioavailability by G2 and G3 generation positively charged PAMAM dendrimers) .

5) **Dendrimer in transdermal drug delivery-** improvement in solubility and plasma circulation time. PAMAM dendrimer complex with NSAIDs(ketoprofen, Diflunisal) as permeation enhancers[16].

6) **Dendrimers for controlled release drug delivery-** anticancer drugs like methotrexate, adriamycin. These were encapsulated into PAMAM Dendrimers ie, (G3 and G4) modified with PEG monoethylether chains (ie,550 and 2000 Da respectively) attached to their surfaces[29.] Controlled release of flurbiprofen could be achieved by formation complex with amine terminated generation 4(G4) PAMAM Dendrimers.

7) **Dendrimers in targeted drug delivery-** folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains [16] .

8) Dendrimers As Nano-Drugs:

Poly(lysine) dendrimers modified with sulfonatenaphthyl 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) [17.]

9) **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 [30]. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue[17, 28.]

DENDRIMER BASED PRODUCTS:

- VIVAGELTM (Starpharma): In clinical phase II trials, it"s a topical vaginal microbicide, prevents infection by HIV (polyvalent properties).
- Stratus® CS Acute Care TM (Dade Behring) - for cardiac diagnostic testing[6].
- SuperFectTM (Qiagen) - gene transfection agent applicable to a broad range of cell lines.
- Alert ticket(US army Laboratory) - anthrax detection
- Priofect™, Priostar™ and STARBURST (starpharma) - targeted diagnostic, therapeutic delivery for cancer cells[16.]

CONCLUSION

A rapid increase of interest in the chemistry of dendrimers has been observed since the first dendrimers were synthesised. The chemical synthesis and modification of the dendrimer resulted in a wide range of variation in properties. Dendrimers, due to its superior architecture; high level of branching, globular architecture and molecular weight, prove to be a novel and reliable method of drug delivery. Future work is necessary to find out cost effective synthetic strategies with minimum efforts and the relationship between dendrimer-drug molecules for effective commercial utilization of this technology.

The review clearly illustrates the different aspects of dendrimers as novel drug delivery system and there will be accretion in the dendrimers seen as drug delivery systems with the advent of more and more dendrimers used for it.

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