

## DENDRIMER: A NEW APPROACH IN PHARMACY

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### ABSTRACT

Various approaches have been used to enhance the therapeutic effect of the drug with less toxicity as improvement of solubility, preparation of microspheres, microemulsion, liposomes etc. Medicinal chemists initially attempted to address this problem by synthesizing a water-soluble derivative of the drug moiety. But it was observed that small structural changes can often reduce the pharmacological activity of a drug. Dendrimers, a nanoparticles based drug-delivery system have numerous applications in pharmaceuticals such as enhancing the solubility of poorly soluble drugs, enhancing the delivery of DNA and oligonucleotides, targeting drug at specific receptor site and ability to act as carriers for the development of drug delivery systems. There are several applications of dendrimers in catalytic reaction, anticancer drug delivery etc. Synthesis of dendrimer- drug complexes can act novel method for improving bioavailability.

**Keywords:** Dendrimers, Drug delivery, Drug complexes and bioavailability.

### INTRODUCTION

Development of highest bioavailable dosage form of a drug is always being challenge to the research scientist. Various approaches have been used to enhance the therapeutic effect of the drug with less toxicity as improvement of solubility, preparation of microspheres, microemulsion, liposomes etc. In the last decade, the field of preparation of materials with low dimensionality and the investigation of their properties gained more and more importance. Nanotechnology and chemistry has been applied on various platforms such as Targeted and controlled drug delivery, Medical devices, Cell/tissue engineering, Gene delivery, Molecular-tags, Biosensors, bioanalysis.<sup>1</sup>

The field of dendrimers is a rapidly expanding area. Since Tomalia synthesized the first polyamidoamine (PAMAM) dendrimer in 1985, the growth in dendrimer research has increased almost exponentially. Initially efforts were concentrated on developing and adapting new and existing synthetic methods

to provide the tools needed to expand this pioneering area of research. More recently attention has been directed toward the application and functional design of dendrimers including gene delivery systems to catalysts and catalyst support dendrimers can be found in materials chemistry, synthetic chemistry. Dendrimers, a nanoparticle based drug-delivery system have numerous applications in pharmaceuticals such as enhancing the solubility of poorly soluble drugs, enhancing the delivery of DNA and oligonucleotides, targeting drug at specific receptor site, and ability to act as carriers for the development of drug delivery systems. The therapeutic effectiveness of any drug is often diminished by its inability to gain access to the site of action in an appropriate dose. This is often due to the poor solubility of the drug in the body's aqueous environment. Medicinal chemists initially attempted to address this problem by synthesizing a water-soluble derivative of the drug moiety. Unfortunately, even small structural changes

can reduce the pharmacological activity of a drug. It is observed that dendrimers have "container" properties in the solution which makes them analogous to unimolecular micelles with the ability to maintain their structure stable at even higher concentrations of solvents. Study of dendrimer mediated solubilization has been found to be superior to cyclodextrin mediated solubilization.<sup>1,2,3</sup>

### Dendrimer

Dendrimers are an interesting class of macromolecules that have a highly symmetrical, hyper-branched and spherical structure. Dendrimers possess an architecture consisting of: (1) a core; (2) an interior of shells (generation); and (3) an exterior (outermost layer), which often has terminal functional groups (Figure.1). The core determines the size and shape of the dendrimer, the interior determines the amount of void space that can be enclosed by the dendrimer, and the exterior allows growth of the dendrimer or other chemical modification. This unique architecture makes dendrimers monodispersed macromolecules compared to

classical linear polymers. In dendritic structures, the number of terminal groups increases exponentially with a linear increase in the generation of the dendrimer. This relationship limits the ultimate size of the dendrimer due to steric crowding of the terminal groups. Several new branching points are available at each repeating unit in their structure for hyperbranched growth<sup>4-7</sup>.

Polyamidoamine (PAMAM) dendrimers are a newer class of polymer that possess a number of interesting and useful pharmaceutical applications. PAMAM dendrimers have capability of enhancing the solubility of low solubility drugs. They also have potential application for the delivery of DNA and oligonucleotide and as platforms for the development of cancer therapeutics. Dendrimers have been shown to cross cell barriers at sufficient rates to act as potential carrier/delivery systems. Surface engineering has been found to reduce cytotoxicity and enhance transport studies on the mechanism of dendrimer transport across epithelial cells.<sup>8-12</sup>

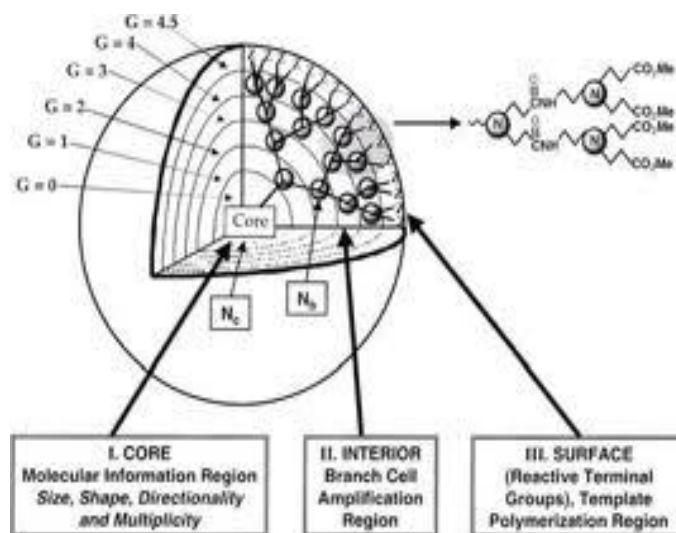


Fig.1: Dendritic structure

### Types of Dendrimers

1. **Pamam Dendrimer:** Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. PAMAM dendrimers are

commercially available, usually as methanol solutions.

2. **Pamamos Dendrimer**

Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of

hydrophilic, nucleophilic polyamidoamine (PAMAM).

### 3. PPI Dendrimer

PPI-dendrimers stand for “Poly (Propylene Imine)” describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vogtle<sup>10</sup>. These dendrimers are generally poly-alkyl amines having primary amines as end groups.

### 4. 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. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

### 5. Multilingual Dendrimers

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

### 6. Chiral Dendrimers

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

### 7. Hybrid Dendrimers Linear Polymers

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

### 8. Amphiphilic Dendrimers

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

### 9. Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes<sup>13</sup> etc.

## DIFFERENCE BETWEEN DENDRIMER AND LINEAR POLYMER

Dendrimers have the characteristic properties unlike the traditional polymers. Because of their molecular architecture, dendrimers show some significantly improved physical and chemical properties. In solution, linear chains exist as flexible coils; in contrast, dendrimers form a tightly packed ball. This has a great impact on their rheological properties. Following is the comparative table for the dendrimers and linear polymer.

**Table 1: Differences between dendrimer and linear polymer**

Property	Dendrimers	Linear polymers
Structure	Compact, Globular	Not compact
Architecture	Regular	Irregular
Size	Certain	Uncertain
Shape	Spherical	Random coil
Aqueous solubility	High	Low
Viscosity	Low	High

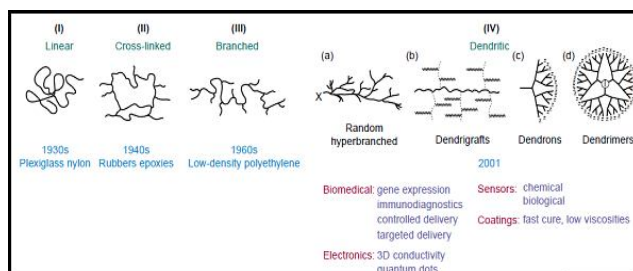


Fig. 2: Macromolecular architecture of polymer and dendrimer

**Synthetic approach of dendrimer**

Dendritic polymers are synthesized using a stepwise repetitive reaction sequence that leads to monodispersed, with a nearly perfect hyper branched topology radiating from a

central core and grown generation by generation. The synthetic procedures developed for dendrimer preparation by controlling the critical molecular design parameters, such as size, shape, surface/interior chemistry, flexibility, and topology.<sup>14,15</sup>

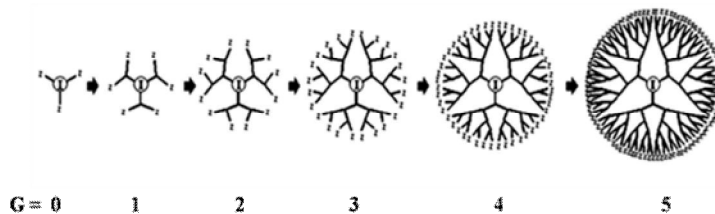


Fig. 3: Structural growth of dendrimer

**Divergent Synthesis**

In the divergent approach, dendrimers are prepared from the core as the starting point and built up generation by generation. In the divergent way, problems occur from an incomplete reaction of the end groups, since these structural defects accumulate with the buildup of further generation. As the side products possess similar physical properties,

chromatographic separation is not always possible. The higher generations of divergently constructed dendrimers always contain certain structural defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. This may cause some difficulties in the purification of the final product.<sup>1,16</sup>

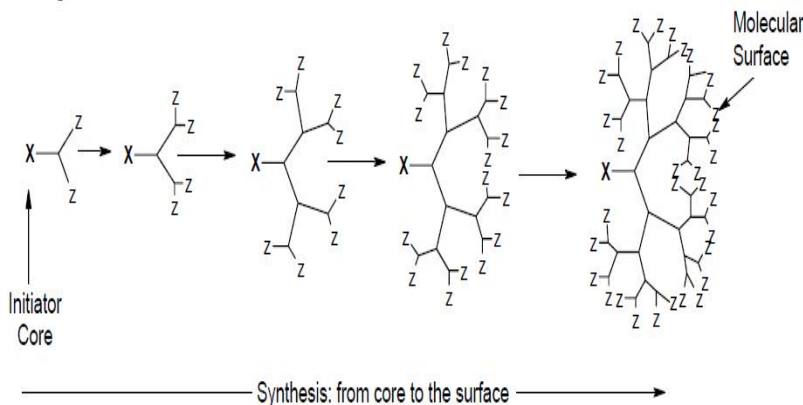


Fig. 4: Divergent synthesis of dendrimer

### Convergent synthesis

The convergent approach starts from the surface and ends at the core, where the dendrimer segments (dendron's) are coupled. In this way, only a small number of reactive sites are functionalized in each step, giving a small number of possible side-reactions per step. In divergent method, purification of the high-generation dendrimer becomes more

difficult because of increasing similarity between reactants and formed product. In convergent method, with proper purification after each step, gives dendrimers without defects. On the other side, it does not allow the formation of high generations because steric problems occur in the reactions of the dendron's and the core molecule.<sup>16</sup>

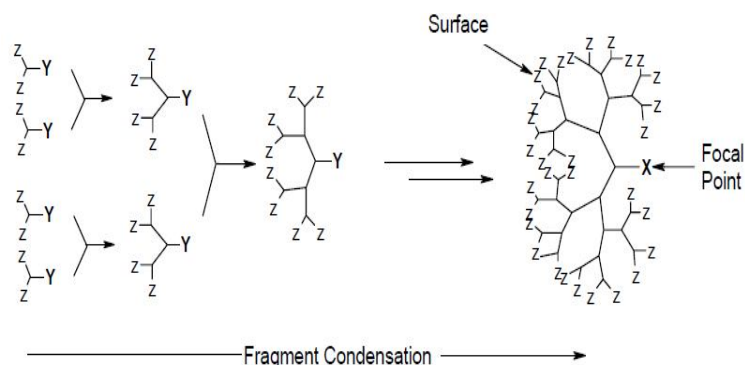


Fig. 5: Convergent synthesis of dendrimer

### Cytotoxicity and dendrimer

Despite the extensive interest in the pharmaceutical applications of dendrimers, there is conflicting evidence regarding their biological safety. Dendrimer having  $-NH_2$  termini shows concentration and generation-dependent cytotoxicity, hemolytic activity. Which are associated with their cationic nature. The cytotoxicity is a function of surface charge, size and concentration. The cytotoxicity and hemolytic activity of cationic PAMAM dendrimer, thought to be the result of the interaction between positively charged dendrimer and negatively charged cell surfaces. The internal structure of dendrimer does not play a main role in toxicity; however, the surface decoration is crucial. Non-charged dendrimer are non-toxic and bioavailable.<sup>17</sup>

### General characterization dendrimer<sup>18</sup>

#### 1. Spectroscopy

##### UV-Visible spectroscopy

Change in structure of dendrimer can be analyzed by UV-Vis spectrophotometer.

##### Infra-red (IR) spectroscopy

Infra-red spectroscopy is mainly used for the routine analysis is of the chemical transformations occurring at the surface of dendrimer.

### Nuclear Magnetic Resonance (NMR) spectroscopy

NMR analysis is especially useful during the step-by-step synthesis of dendrimer, and to detect structural changes after dendrimer interaction with drug. It informs about the chemical transformations undergone by the end groups.

### 2. Microscopy

Two types of microscopy can be used to image dendrimer. In Transmission Electron Microscope (TEM), electrons or light produce images that amplify the original one, with a resolution ultimately limited by the wavelength of the source. The images are produced by touch contact at a few angstroms of a sensitive cantilever arm by Atomic Force Microscopy (AFM) visualizing single molecules by optical microscopy has been successfully carried out for dendrimers having a fluorescent core.

### Size exclusion chromatography (SEC)

Size exclusion chromatography (SEC) allows the separation of molecules according to size. The polydispersity, which is generally very close to unity, determined by SEC.

Dendrimers prepared by using different generations of dendrimer can be separated by using SEC techniques.

### 3. Rheology, physical properties

#### **Intrinsic viscosity**

Metallodendrimers should exhibit maximum intrinsic viscosity according to generation, because the volume grows faster with generation than the molecular weight whereas the opposite phenomenon occurs after a certain generation. This behavior is experimentally observed for several series of dendrimers.

#### **Differential Scanning Calorimeter (DSC)**

Glass transition temperature ( $T_g$ ) depends on the molecular weight, entanglement and chain-end composition of polymers which determined by DSC technique. The  $T_g$  is affected by the end group substitutions, and the molecular mass. DSC and temperature modulated calorimetry (TMC) can also be used to detect physical aging of dendrimer.

### 4. Miscellaneous

Identification of dendrimer was done by subjecting the plain and PEGylated dendrimer to reaction of  $\text{CuSO}_4$  solution. Some other techniques used for characterizing functionalized dendrimers are titrimetry to determine the number of  $\text{NH}_2$  end groups of PAMAM dendrimers.

## APPLICATIONS OF DENDRIMER

Surface functionalized dendrimer have attracted a great deal of attention recently and their study is becoming a growing field because of their unique physicochemical properties as discussed further.

### 1. Advancement of drug delivery

Drug molecules are either chemically conjugated to the dendrimer surface or physically encased inside a dendrimer core. For chemical conjugations, a good coupling efficiency can be achieved by activation of functional groups prior to coupling. Hydroxyl (OH), carboxyl (COOH), primary amine ( $\text{NH}_2$ ), thiol (SH) and guanidine are commonly found functional groups in drug molecules and polymers. Hydroxyl groups are converted to active intermediates that favor nucleophilic reactions. For example, coupling hydroxyl groups with primary amine groups causes groups to form secondary amines or stable carbamate bonds. Amides are relatively stable

in basic, acidic and enzymatic conditions. In some cases, direct coupling may lead to the deactivation of drugs, so that the conjugated drugs (i.e., prodrugs) will not have any therapeutic effect until they cleaved from the bonding. PAMAM dendrimers forms conjugate with 5FU, which is water-soluble and releases free 5FU slowly on hydrolysis of the conjugate reducing the toxicity<sup>8,9</sup>.

### 2. In catalytic reactions<sup>19</sup>

Dendrimer catalyst analogues have highest catalytic activity. The cavities provide nanoscale reactor sites for catalysis. Core, surface are two possible catalytic sites in dendrimer.

### 3. Complexes with metal as antimicrobial

Even generations of PAMAM dendrimer having cationic charges over their surface are responsible for cell membrane lyses, which help to metal ions to effectively act on microbial and fungal cells.

Dendrimer-silver complex nanocomposite is an effective antimicrobial agent tested *in vitro* on *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* bacteria using the standard agar overlay method. It shows better antimicrobial activity even in the presence of sulphate or chloride ions. It shows that dendrimers with polyamine surfaces that are partially modified by hydrophobic groups effectively bind and sequester bacterial lipopolysaccharides *in vitro* as well as *in vivo* models of septic shock.

### 4. Targeted drug Delivery<sup>20</sup>

Surface dendrimers are a time-release vehicle for biologically active agents. They offer higher activity and longer duration of action, than small molecule through polyvalent interactions. Branching of poly (L-glutamic acid) on PAMAM dendrimer gives new biodegradable polymers with improved bio distribution and targeting ability. These constructs were surface-terminated with polyethylene glycol chains to enhance their biocompatibility, and folic acid receptors to introduce cell specific targeting.

### 5. Gene therapy as delivery tool<sup>21</sup>

Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. PAMAM dendrimers tested as vectors.



Dendrimers are very active under investigation for the delivery of DNA and small organic molecule drugs, especially for cancer therapy. PAMAM and PPI dendrimers enhances the transfection efficiency of DNA. It is noteworthy that dendrimers of high structural flexibility and partially degraded hyper-branched architectures appear to be better suited for certain gene delivery operations than intact high-generation symmetrical dendrimers. They form more compact complexes with DNA. The maximum transfection efficiency is because of net positive charge on the complexes (i.e., an excess of primary amines over DNA phosphates). Interior tertiary amine groups of PAMAM-OH dendrimers (hydroxyl-terminated polyamidoamine, PAMAM) were modified by methylation to make these polymers have a more cationic character, which enabled electrostatic interaction between PAMAM-OH and plasmid DNA.

#### 6. Contrast agent<sup>22</sup>

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

#### 7. Electronic nanodevices<sup>23</sup>

Dendrimers have applications in molecular electronics and photochemical molecular devices. PAMAM dendrimer forms stable interior nanocomposites with metal cations, zero valent metals, other electrophilic ligands and semiconductor particles. The multifunctionality and biocompatibility of dendrimer-based nanodevices are crucial for the development of targeted drug delivery technology. PAMAM dendrimers act as a carrier in multifunctional cancer therapeutic nanodevices.

#### CONCLUSION

The chemical synthesis and modification of the dendrimer resulted in a wide range of variation in properties. Hence their different application are possible. This novel class of polymers and their derivatives exhibit unique physicochemical and biological properties, which have great potential for pharmaceutical and other use in a variety of applications. 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. It may work worthy in targeted drug delivery and treatment of diseases like cancer.

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