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## Multifunctional Dendrimeric Drug Delivery: A Novel and Challenging Drug Delivery System

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### ABSTRACT:

Multifunctional dendritic polymer (also known as dendrimer) mediated drug delivery system is aimed at providing effective drug delivery at the target site. This system exhibits low toxicity, high solubility of drugs, high loading capacity and stability in biological environment. Cell specificity is achieved by functionalizing the surface of dendritic polymer by targeting ligands. The multi-valent property of this drug delivery system increases the binding strength of the polymer with the corresponding cell. The article reviews the advantages of Multifunctional Dendrimers in Drug Delivery system, also briefs formulations of drugs using dendrimers.

**KEYWORDS:** Dendrimers, Dendritic polymers, Multifunctional polymers, Dendrimeric drug delivery, Branched polymers.

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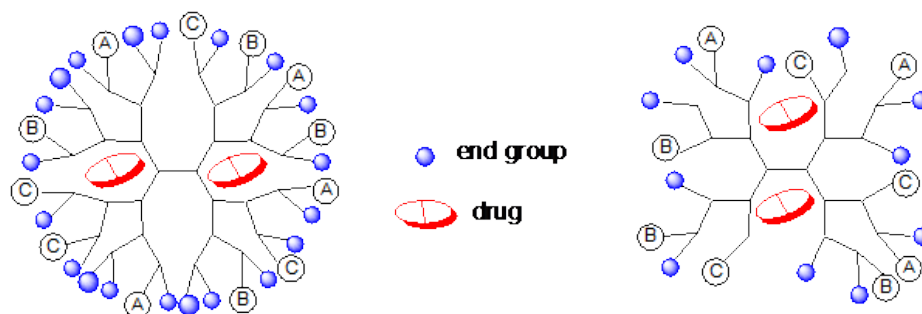
### INTRODUCTION:

Dendritic polymers are highly branched exhibiting tree-like structure. These are symmetric; size can be measured in nanometers.

### Structure of dendrimer

These possess a central core continued with repeating units and terminal functional group.

The polymers constitute nano-cavities from the interior where drugs are encapsulated or conjugated.



The schematic representation of multifunctional dendrimer (left) and hyperbranched polymer (right). End groups A, B, C depict the presence of targeting ligands, protective coating, transport agents, fluorescent probes, or a drug conjugated on the surface of the dendritic carrier.

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## Functions of different end groups

Targeting ligands are responsible for specificity of the drug carrier; protective agents keep the dendrimer stable in the biological milieu. Transport agents facilitate distribution of drugs. Each type of external group plays an important function. Thus, specificity to certain cells has been achieved by surface attachment of targeting ligand. Folate targeting ligand [1-2], due to its simple structure and convenience of surface attachment is extensively used.

## ADVANTAGES OF DENDRIMERIC DRUG DELIVERY

1. Dendrimers possess multiple functions owing to their ability to carry agents such as targeting ligands, fluorescent probes etc.
2. Dendrimers are nano-carriers, with cavity at the centre. The drugs are encapsulated or conjugated within the cavity, providing protection and stability to the system.
3. Dendrimeric drug delivery system plays an important role in the treatment of diseases like carcinoma, owing to its targeting ability and specificity to cancerous cells.
4. Branched structure of dendrimers provides large surface area for the attachment of dendrimer with other agents such as ligands or the cell surface intended.

## TYPES OF DENDRIMERS [3, 4, 5, 6]

### 1. Pamam Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting with ammonia or ethylenediamine initiator core reagents.

### 2. Pamamos Dendrimer

Radially layered poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine interior surface and hydrophobic organosilicon exterior surface.

### 3. PPI dendrimer

PPI is an abbreviation for poly (propylene imine). These possess primary amines as end groups. The core structure is usually Diamino Butane (DAB) based.

### 4. Chiral dendrimers

The chiral nature of these dendrimers is due to the constitutionally different but chemically identical branches attached to the core.

### 5. Micellar dendrimers

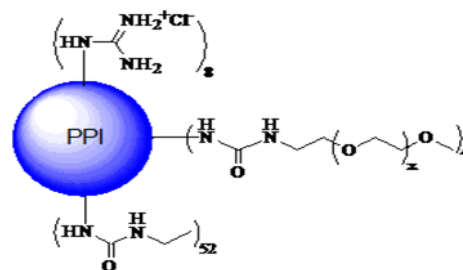
These are micelles of water soluble polyphenylenes. These are hyperbranched and unimolecular in nature.

## 6. Multilingual dendrimers

The surface of these dendrimers constitutes multiple copies of a particular functional group.

## MATERIALS AND METHODS OF DRUG DELIVERY

- A. Using diaminobutane polypropylene imine (PPI) with 64 end amino groups, a sample multifunctional dendrimeric drug delivery system was produced [7]. This provides stability, prolonged circulation, greater solubility and binding strength. This system transports drug through cell membrane to which it is bound and offers pH-sensitive drug release. pH-sensitive drug release is due to polyamine character of nanocavity. By reducing number of toxic amino groups toxicity of the system is reduced.



multifunctional dendrimeric derivative based on diaminobutane poly propylene imine. Dendrimer with 64 end groups.

- B. Boltorn H40 was functionalized using poly (ethylene glycol) chains with a water soluble PEGylated dendritic derivative, BH40-PEG [8]. PEGylation of the dendritic scaffold is compulsory not only for protecting the drug carrier in biological fluid but also for improving its water solubility. Paclitaxel solubility increases by a factor of 65, 110, 210 and 350, in 1%, 3%, 6% and 9% w/v BH40-PEG solutions respectively, compared to its solubility in water. Paclitaxel simulated release was determined by the dialysis method and showed that about 60% of the encapsulated drug was released in the aqueous phase during the first 6 hours and almost completed in 12 hours time period. The cytotoxicity was assessed *in vitro* with A549 human lung carcinoma cells and found to be non-toxic for 3h incubation at concentrations equal to or lower to 50  $\mu\text{M}$ , while  $\text{LD}_{50}$  was 100  $\mu\text{M}$ .
- C. In another report; [9] herceptin targeting ligand was used i.e. a humanized monoclonal antibody binding to human growth factor receptor-2. It was covalently attached to a fifth-generation PAMAM which was also conjugated with methotrexate anticancer drug. In addition, binding and

uptake of these antibody conjugated dendrimers was blocked by excess non-conjugated herceptin. Decreased cytotoxicity of the conjugate in comparison to free methotrexate was attributed to the slow release of methotrexate from the carrier and its long retention in the lysosomes. Although the conjugate was less toxic to cells than free methotrexate *in vitro*, it is however possible that this carrier might be superior for *in vivo* experiments due to its decreased toxicity for HER2-overexpressing breast cancers as a result of its specificity to target tumor cells.

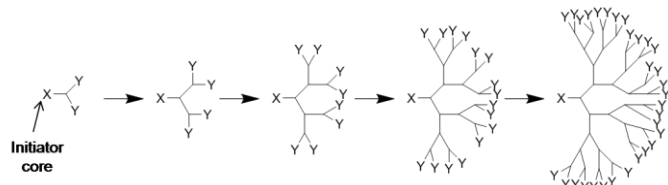
### SYNTEHESIS OF DENDRITIC POLYMERS [10]

Dendrimer is synthesized by employing three methods mainly viz;

1. Divergent method
2. Convergent method
3. Click chemistry

#### 1. Divergent method

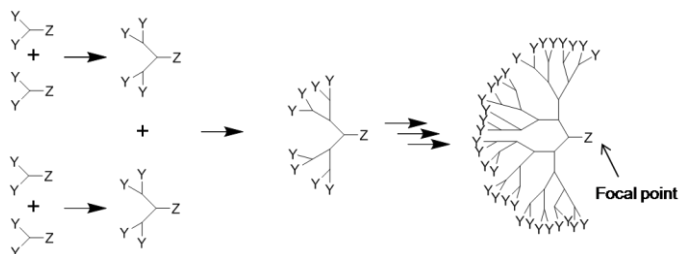
Using divergent method dendrimer is synthesized by elongating the chain from the central multifunctional core towards exterior by Michael reaction.



The reaction is carried out till its completion to avoid incorrect dendrimers. Improper dendrimers have variation in the length of the branches. i.e; some branches are shorter compared to other branches. It is difficult to separate them as there is no much difference in the sizes of the dendrimers as a whole.

#### 2. Convergent method

In this method the dendrimers are synthesized by elongating the chain towards central multifunctional core towards interior.

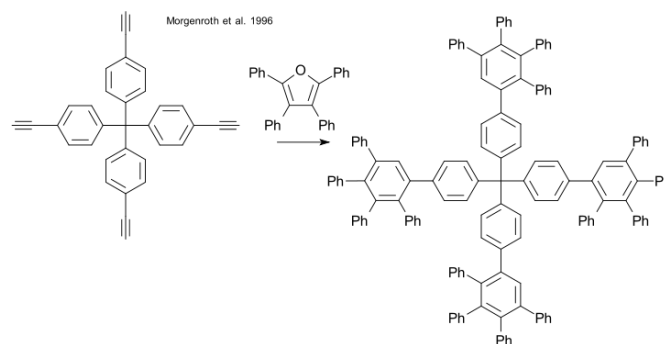


By this method, uniform dendrimers can be synthesized but large dendrimers cannot be prepared because of the steric hindrance.

#### 3. Click chemistry

Dendrimers can be prepared by click chemistry using Diels-Alder reaction, Azide-Alkyne and thio-lyne reactions.

An example of Diels-Alder reaction is as follows.



Tetra-benzene precursor      Poly-Phenyl Dendritic polymer

### APPLICATIONS OF DENDRIMERIC DRUG DELIVERY

1. Dendrimers are used as adhesives for sutureless ophthalmic surgery. Grinstaff et al [11, 12] have developed dendrimer based biodegradable sealants for ophthalmic surgical applications.
2. These are used in medical imaging systems. [13] Dendrimeric systems are used as nanoprobe for nuclear magnetic imaging both for Single Photon Emission Computed Tomography (SPECT) (<sup>99m</sup>Tc, <sup>111</sup>In, <sup>125</sup>I) and Positron Emission Tomography (PET) (<sup>68</sup>Ga).
3. Dendrimers are used as solubility enhancers to increase the solubility of poorly-soluble drugs like Anthelmintic Benzimidazole carbamate for the effective treatment of worm infections [14].
4. Dendrimers are used for photodynamic therapy. Macromolecular dendritic derivatives are capable of delivering 5-ALA efficiently to cells for sustained porphyrin synthesis as a photodynamic therapy. [15]
5. Delivery of Anti-Cancer drugs is done using dendritic polymers [16]

A biocompatible polyester dendrimer composed of the natural metabolites, glycerol and succinic acid, is described for the encapsulation of the antitumor camptothecins, The cytotoxicity of the dendrimer-drug complex toward four human cancer cell lines [human breast adenocarcinoma (MCF-7), colorectal adenocarcinoma (HT-29), non-small cell lung carcinoma (NCI-H460), and glioblastoma (SF-268)] is seen. Cellular uptake and efflux measurements in MCF-7

cell show an increase of 16-fold for cellular uptake and an increase in drug retention within the cell when using the dendrimer vehicle.

## CONCLUSION

Dendrimeric drug delivery possesses a promising future owing to its applicability in the field of pharmacy and biomedical sciences. It is a useful tool for diagnosis as well as drug delivery. Its branching, multi-functionality, stability, well-defined molecular weight etc provide new scaffold for drug delivery. Dendrimers can also prove useful for enhancing the solubility of poorly-soluble of drugs, hence providing scope for better pharmacokinetics of the drugs. Future may witness increasing number of commercially available dendrimeric drugs.

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