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Dendrimers- Emerging Polymers for Drug Delivery and Its Future Prospects

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ABSTRACT

Polymeric drug delivery system can enhance bioavailability, therapeutic efficacy and decrease the side effects of drugs. Past polymer technologies focused mainly on linear polymers. Currently, highly branched polymers have been found whose properties are different from conventional polymers. Of these polymeric Drug delivery systems, Dendrimers are more potential now-a-days. The following article deals with all aspects related to Dendrimers like goals, methods of synthesis, bioavailability studies, applications, and their future prospective. It also deals with recent advances in dendritic polymer based Drug delivery system.

Keywords: Dendrimer, PAMAM, PPI, core, branching units

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INTRODUCTION

The term Dendrimer is derived from Greek words “Dendron” meaning tree and “meros” meaning part. The synonyms for Dendrimer are arborescences and cascade molecules. Dendrimers are well-defined, extensively branched macromolecules radiating from central core and synthesized through repetitive reaction sequence in stepwise manner. Dendrimers consists of an internal core, branching units and branches. The drug remains undamaged within the Dendrimers which increase its stability, solubility and controlled release from matrix suggesting encapsulation with Dendrimers as a general approach [1-3].

GOALS OF DENDRIMERS

Drug delivery is very crucial aspect of formulation as its choice control bioavailability, concentration profile and side effects. Though most drugs are given in oral route, it must be stable in conditions like p^H , enzyme activity. Thus a suitable DDS (Drug Delivery System) would protect drug against degradation which is satisfied by dendrimers [4]

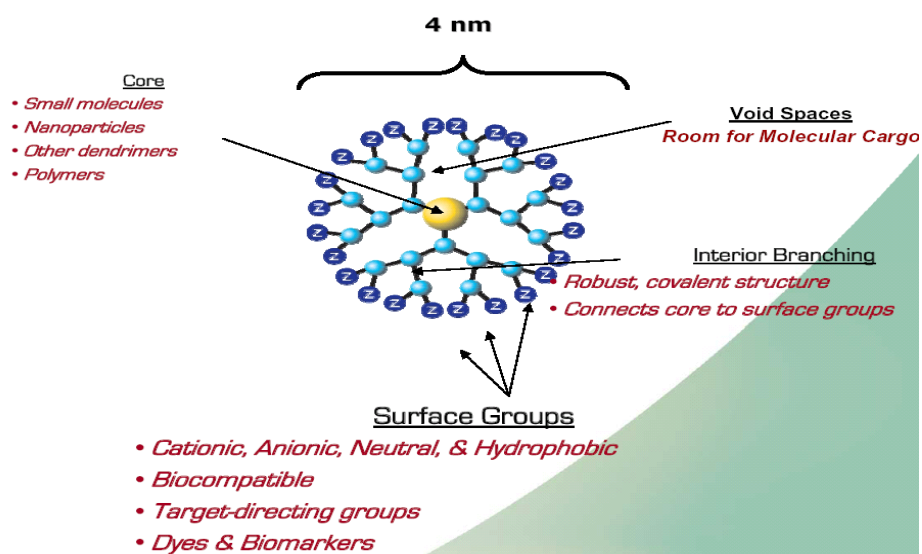
Goals of Dendrimers include

1. Modifying PK (Pharmacokinetic) & PD (Pharmacodynamic) properties of drug
2. Achieve controlled and targeted release of drug restricted to area desired

COMPONENTS OF DENDRIMER STRUCTURE [5]

The structure of a dendrimer consists of following components.

Figure 1: Components of Dendrimer



Generation: It is the hyper branching; the number of branching or focal points from core to the dendrimer surface is the generation number. The core part of dendrimer is sometimes called as generation 'zero' or G_0 .

Shell: It is the homo-structural spatial segment between the branching points, the 'generation space'

Outer shell refers to space between last outer branching point and surface where as inner shell refers to interior of dendrimer.

Pincer: Outer shell consists of number of pincers formed by last focal point before reaching dendrimer surface

End group: Terminal or surface group

PROPERTIES OF DENDRIMERS [6 -9]

Dendrimer properties are dominated by the functional groups on the surface. Recently redox-active nanoparticles can be synthesized where redox molecules are placed between core and dendritic wedges.

Volume of dendrimer increases when it has positive charge. This property is applied in using dendrimers for DDS which give medication directly to affected part inside patient's body.

Table1: Properties of Dendrimers

PROPERTY	DESCRIPTION
1.Monodispersity	Dendrimers are constructed with well defined molecular structure. Verified by HPLC,SEC ,MS,GE
2.Nanoscale size and shape	Dendrimers are often referred to as artificial proteins owing to their narrow size distribution and other biomimetic properties
3.Polyvalency	It shows outward presentation of reactive groups on exterior of dendrite structure. Based on type of functional group attached to tips of branches ,participate in multiple interactions with biological receptors
4.Physico-chemical properties -High multivalent surface -Low p^H -Neutral p^H	High number of functional groups exposed on surface Extended spectrum due to electrostatic repulsion between positively charged ammonium groups Back folding occurs due to H-bonding between unchanged tertiary amine in interior and positively charged surface amines

$-p^H \geq 10$	High degree of back folding
5. Biocompatibility	Dendrimers should be <ul style="list-style-type: none">-non toxic-non-immunogenic-bio permeable-retain in circulation for intended time-able to target specific structure

SYNTHESIS

Two major strategies were reported for dendrimer synthesis. The first was called as “divergent method” in which dendrimer grows from core site. The second method was “convergent method” where number of dendrons reacts with multifunctional core to get a product. Another method was also introduced by Frechet and team called “double-stage convergent method” where divergent approach is followed by convergent assembly giving rise to orthogonally protected trimer.

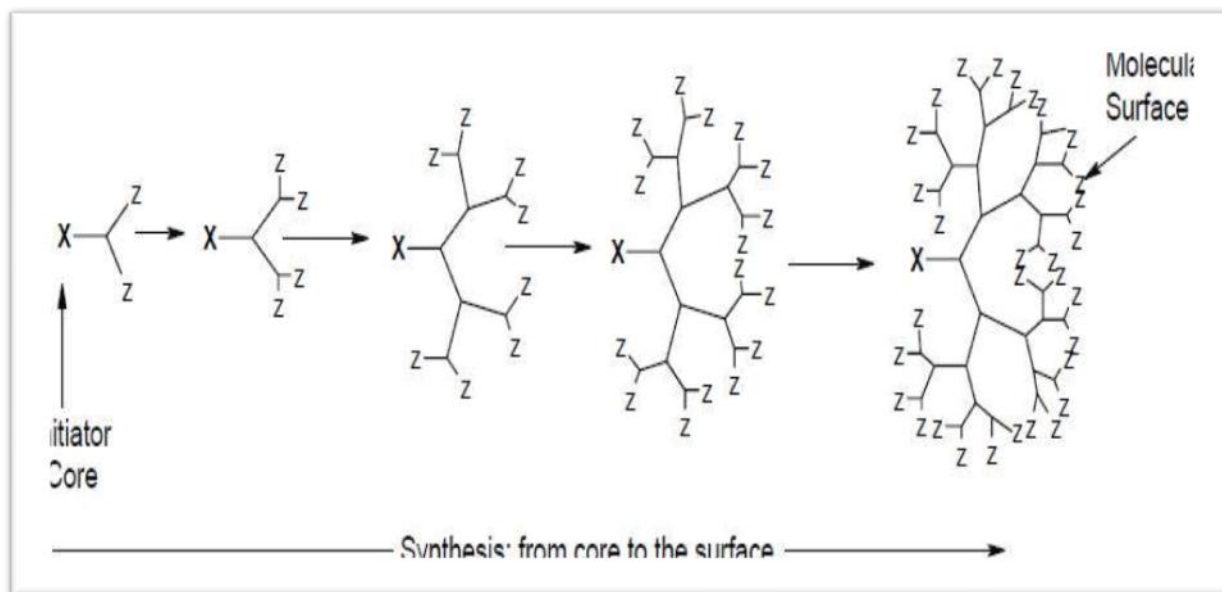
Divergent method [10]:

It is the strategy currently preferred.

In this method, the core is reacted with 2 or more moles of reagent with at least 2 protecting branching sites followed by withdrawal of protecting groups. The liberated reactive site leads to first generation dendrimers. The process is repeated until desired size is obtained.

The core may be either ethylene diamine or ammonia or cystamine. Initially alkylation of primary amines of core occurs with methyl acrylate followed by amidation of amplified ester groups with large excess of ethylene diamine. This produces G_0 series with primary amine terminal groups. Each amino group in turn reacts with 2 additional molecules of methyl methacrylate monomers followed by reaction with 2 or more ethylene diamine molecules to produce first generation dendrimers.

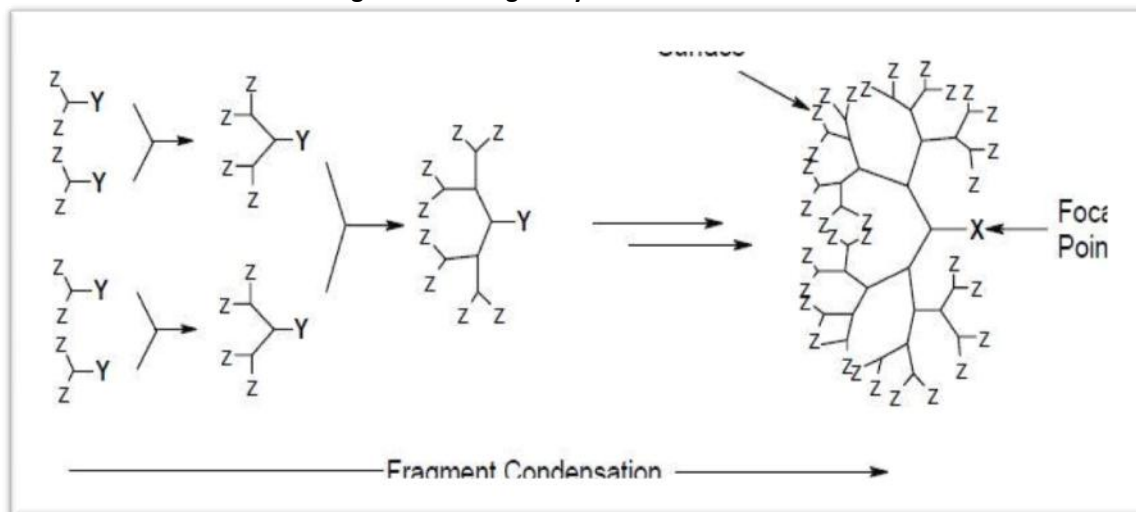
Figure 2: Divergent synthesis of dendrimers



Convergent method [11]:

Here growth of dendrimer starts at periphery with branching units and ends at the core by linking surface with more monomers. This strategy is limited to only lower generation dendrimers on account of nano scale steric issues and low yields.

Figure3: Convergent synthesis of dendrimers



TYPES OF DENDRIMERS [12-19]

Commercially available dendrimers

Starburst (PAMAM)

Astramol(PPI)

Table2: Types of dendrimers

Types	Characteristics
1.Liquid crystalline	Formed by functionalization of end group of carbosilane dendrimers with 36mesogenic units
2.Tecto	Composed of core dendrimer with or without therapeutic agent surrounded by several types of dendrimers
3.Chiral	Find application in asymmetric catalysis&chiral molecular recognition
4.PAMAMOS (polyamidoamine-organosilicon)	Inverted unimolecular micelles consisting of hydrophilic,nucleophilic PAMAM interiors and hydrophobic organosilicon exterior
5.Peptide	Framework of traditional dendrimers with peptides on surface incorporating amino acids as branching units
6.Glycodendrimers	Dendrimers incorporated with carbohydrates in their structure Used for protein-carbohydrate interactions
7.PPI (propyleneimine)	Poly alkyl amines having primary amines as end group
8.Pamam	Formed by divergent method starting with ammonia or ethylenediamine core Commercially present as methanol solutions
9.Multilingual	Contains multiple copies of particular functional group on surface
10.Hybrid	Combination of dendritic and linear polymers in hybrid block
11.Amphiphilic	End of chain consists of 2 sites ,one half is e^- donating &other is e^- withdrawing
12.Micellar	Unimolecular micelles of water soluble hyper branched polyphenylenes
13.Multiple antigen peptide dendrimer	Possess multiple antigens

DENDRIGRAFT POLYMERS [20]

These are most recently discovered structures larger than dendrimers and grow much faster &lify surface groups more dramatically as a function of generational development.

It involves iterative grafting of oligomeric reagents derived from living polymerisation process in various graft-on-graft strategies. Each grafting step is called as generation.

MECHANISMS OF DRUG ATTACHMENT WITH DENDRIMERS [21, 22]

These include

1. Encapsulation:_Guest drug molecules are directly encapsulated into ellipsoidal, empty internal open cavities of dendrimers. Eg: 6-mercaptopurine, camptothecin.

2. Covalent interaction: Owing to the presence of functional groups on the surface, drug molecule with specific functional group is attached covalently to dendrimers. Eg: Propranolol to third generation dendrimers.

3. Electrostatic interactions: Functional group on surface is expected to enhance solubility of hydrophobic drugs by electrostatic interactions owing to their high density. Eg: Nicotinic acid, NSAID.

BIO-COMPATIBILITY STUDIES [23, 24]

In-vitro

1. Cytotoxicity and dendrimers

Dendrimers having terminal amino group shows concentration and generation dependant cytotoxicity, haemolytic activity both of which are associated with cationic nature. Cytotoxicity results due to surface charge, size and concentration.

2. Haemolytic activity

These assays give quantitative measure of Hb release which correlates to amount of RBC lysis.

3. Endocytic uptake

Dendrimers are transcytosed across epithelial tissue which mechanism is unknown.

In-vivo

- Bio distribution
- General toxicity
- Immunogenicity

Invitro and in vivo studies revealed that nanoparticles possess long circulation times & low RES uptake. Penn State Researchers developed novel synthesis process & compositions of intelligent polymers (IP) both of which are biodegradable and thermal responsive.

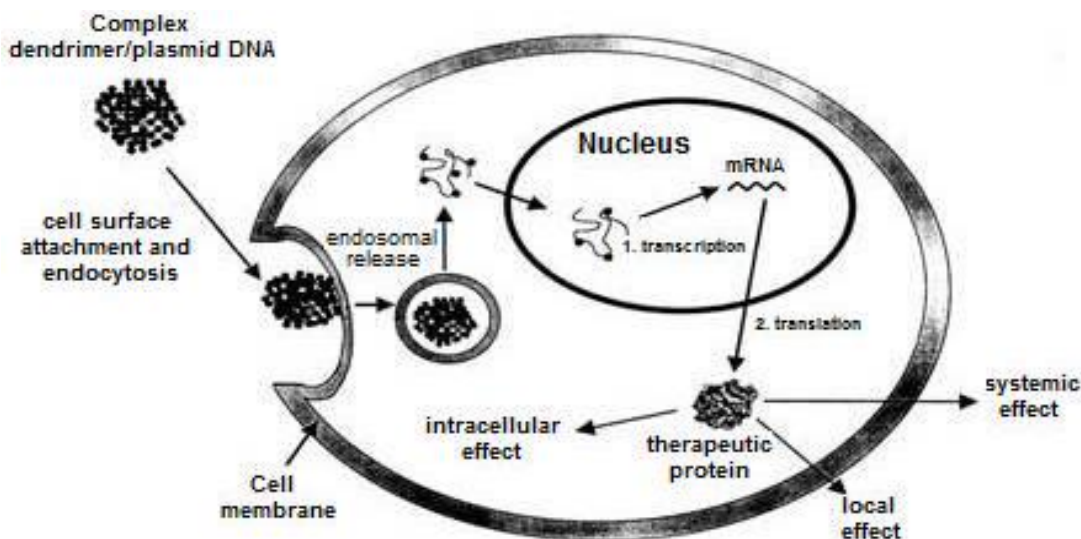
IP composed of poly (N-isopropyl acryl amide) (PNIPAAM) as thermal responsive unit, poly (L-lactic acid) (PLLA) as biodegradable hydrophobic unit & p^H sensitive poly (L-lysine) (PLL) dendron domain.

APPLICATIONS OF DENDRIMERS

1. Pharmaceutical applications [25-28]

- a. Ocular drug delivery - useful for delivery of drugs to eyes due to greatly enhanced permeation of drug through cornea by dendrimers.
- b. Targeted drug delivery - owing to the presence of many functional groups ,multiple ligands can be attached facilitating target to tumour surface or other.
A novel sustained release DDS was demonstrated by researchers at Mayo clinic where dendrimers allow delivery of sterols to targeted cells which cause damage through neuroinflammation resulting in retinitis pigmentosa & dry age associated macular degeneration both of which gradually damage retina and ultimately cause vision loss.
- c. Controlled drug delivery - dendrimer encapsulate drug into its cavity from which the drug is released in controlled manner.
- d. Pulmonary drug delivery - positively charged PAMAM dendrimers increased relative bioavailability of pulmonary Drug Delivery of Enoxaparin
- e. Transdermal drug delivery - dendrimers improve solubility plasma circulation time via transdermal formulations & deliver drugs to high water soluble nature.
- f. Oral drug delivery.
- g. Biomimetic artificial proteins - due to their narrow size distribution and other properties.
- h. Nano scaffolds.
- i. Nano drugs.
- j. Bioavailability enhancer - due to solubility & permeability enhancement, help in permeation of drugs administered topically. Increase in permeability depends on concentration and generation size of dendrimers.
- k. Gene delivery - dendrimers possess the ability to form compact complexes with DNA, the property which makes them non-viral vectors for gene delivery.
The performance of these vectors depends on physicochemical and colloidal properties. The mechanism is shown in figure 4.

Figure4: Dendrimer involved in gene transfection



2. Therapeutic applications [28, 29]

a. Dendrimers in Photodynamic therapy

Cancer treatment involves administration of light activated photo sensitising drug that concentrates in diseased tissue selectively

b. Dendrimers for boron neutron capture therapy(BNCT)

Radiation energy generated from capture reaction of low energy thermal neutrons by 10 boron atoms has been used successfully for selective destruction of tissue

c. Complexes with metals as Anti-microbials

PAMAM dendrimer with cationic charges over their surface are responsible for lysis of cell membrane which help metal ions to act effectively on microbial and fungal cells

3. Diagnostic applications [28]

a. X-Ray & MRI contrast agents

These became important tools of modern diagnostic medicines. Dendrimers possess multiple binding sites on periphery allowing many contrast agents to form complexes with dendrimers

b. Catalysts/enzymes

c. Molecular probes

RECENT ADVANCES OF DENDRITIC POLYMERS [30, 31]

1. Targeting dendrimers to HIV infected macrophages in vitro

Monocytes and macrophages disseminate HIV throughout body and targeting of these cells treat HIV. Tuftsin is a macrophage activator tetra peptide which bind specifically to monocytes and macrophages. In this work Dutta et al. prepared efavirenz (EFV) loaded, tuftsin conjugated fifth generation PPI to study their anti-HIV activity in vitro. Entrapment of EFV in polymer was found to be 0.87g of EFV per g of TuPPI, ...with entrapment efficiency of 49%. Without tuftsin the entrapment efficiency is 37%. Increase in efficiency is due to increased functional group available for complexation.

2. Plasmid & Doxorubicin co-delivery targeting to tumour

PEGylated PAMAM dendrimer with tumour targeting moiety (peptide HAMPRH (T7)) was used to deliver tumour necrosis factor related apoptosis inducing ligand & Doxorubicin, a common anticancer drug

FUTURE PROSPECTS OF DENDRIMERS [32]

Though very few pharmaceutical products having dendrimers are available in market, the dendrimer technology holds great potential adding value to pharmaceutical products.

Future development focuses on following aspects

- a. Reducing cost of synthesis of dendrimers so as to be applied extensively in membranes & other fields.
- b. Enlarging application of membranes from hyper branched polymers to the fields of resources and environment.
- c. Exploiting new applications of dendritic polymers in other fields of membrane.

CONCLUSION

Dendrimers are an excellent drug delivery system and holds promising future in various fields like pharmaceutical, therapeutic, and diagnostics due to their characteristics like versatility, condensed structure and ability to recognise specific tissue and also their high degree of branching, multivalency etc., The cytotoxicity of dendrimers can be overcome by careful surface engineering. Significant advances and innovations have resulted in a wide range of dendritic architecture & delivery methodologies that promise to become an integral part of future medicine. As research progresses, newer applications of dendrimers will emerge and future depends on dendrimer based drug delivery system.

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