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DENDRIMER: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Dendrimer as a drug delivery agent is a promising, safe and selective drug delivery option. It's highly selective nature for targeting the desired tissue is the most essential property and holds a promising future for the treatment of several disorders. Its other properties like very small size, polyvalency, monodispersity, stability make it an appropriate carrier for delivering drugs with precision and selectivity. Dendrimers are being used as drug delivery systems for various drugs like anticancer drugs (methotrexate), drug for prevention of HIV, enhancing bioavailability of pilocarpine for ocular drug delivery, et al. Dendrimer as a drug delivery system is based on the approach of sending a nanoparticle (10^{-9}) to the body, loaded with drug. The drug might be loaded on its terminal surface or encapsulated within the branches of a dendrimer. Dendrimers help in achieving increased bioavailability, sustained, controlled as well as targeted release of drug. There is reduction in the amount of drug and systemic toxicity while the therapeutic efficacy increases. This approach as a drug delivery system certainly promises a reliable, safe, selective and precise method of drug delivery. Thus present review focuses on the fundamentals of dendrimers and their use as drug delivery agents in treatment of disorders.

Keywords: Dendrimers, nanoparticle, novel drug delivery, target delivery

INTRODUCTION

Drug delivery is a vital aspect of formulation as its proper choice controls the bioavailability, concentration profile and side effects (by targeted drug delivery) [1]. While the most compliant way of drug administration might be its oral, it requires that drug is stable in conditions for example: pH, enzyme activity, epithelial permeability. Example, Insulin- peptide drug will be normally degraded by the digestive enzymes[1]. Thus, a suitable drug delivery system would protect the drug against degradation and ensure that drug reaches proper permeability properties and further provides a combined transportation and protection system against the natural barriers, as done by the dendrimers[1]. Dendrimers are highly defined nanoparticles:

– Size: 1 -15 nanometers
– Very versatile surface functionalisation
– Synthetic: Practical and cost effective
– Well tolerated pharmaceutica

What is a dendrimer?

Dendrimer is a nanoparticle (10^{-9}) and so has advantages over microparticles or others due to its small size, easy uptake by cells (through endocytosis)[1]. They are branched macromolecules have a central core unit having a high degree of molecular uniformity, narrow molecular weight, distribution, specific size and shape characteristics, and a highly- functionalized, terminal surface. 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[2]. Dendrimers have cellular uptake through endocytosis and thus brings drug 'bound' to dendrimers into the cell[1].

Goals:

A) Modify/Improve the pharmacokinetic and pharmacodynamic properties of a drug so that there is also an accretion in bioavailability.

B) Achieve the controlled and targeted release of drug restricted to the area desired.

Expectations:

The reduced size provides increased surface area to volume ratio properties[3]:

A) Optical properties, e.g. fluorescence, become a function of the particle diameter (control in size).

B) When brought into a bulk material, nanoparticles can strongly influence the mechanical properties, such as rigidity and strength.

Example, traditional polymers can be reinforced by nanoparticles resulting in novel materials; e.g. as light weight replacements for metals. Therefore, an increasing societal benefit of such nanoparticles can be expected.

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Table 1: Generation and corresponding structure of dendrimers[4]

Generation of dendrimers	Structure
First three	Small, not specific three dimensional structure
Fourth (G4)	Beginning to become spherical, to a preferred three dimensional structure
Fifth (G5)	Highly structured spheres

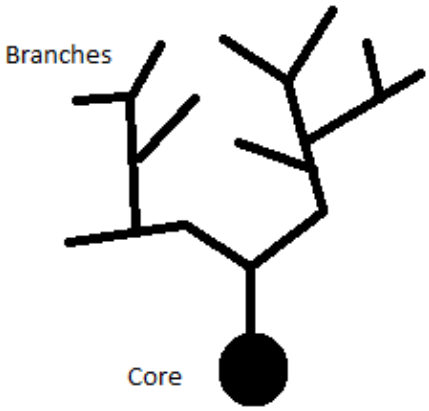

Figure 1: Sturcture of a Dendrimer

SYNTHESIS OF DENDRIMER

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

A) **Divergent growth method** (introduced by Tomalia)[4] Growth of dendrimers originates from a core site. Process is repeated until the dendrimer of the described size is obtained

B) **Convergent growth method**[18]**-** 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.
An advantage of convergent growth over divergent growth stem: Two simultaneous reactions are required for any generation-adding step[5].

C) **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[6]

D) **Double Exponential' growth-** monomers are prepared from a single starting for divergent and convergent growth. Resulted two products reacted to give orthogonally protected trimer, which can be used to repeat the growth again[6].

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)[2,7,8].

There are broadly two mechanisms for drug delivery.

A) First, is by in vivo degradation of drug dendrimer conjugate (covalent bonding of drug to dendrimer), which depends on presence of suitable enzymes or an environment capable of degrading bonds.

B) The second one is by releasing the drug due to changes in physical environment such as pH, temperature. This approach is independent of the external factors and takes place in cavities of the core (endo-receptor) or outer shell of receptor (exo-receptor)[1].

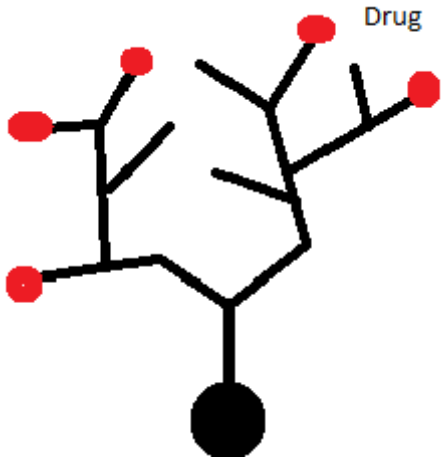

Figure 2: A Dendrimer molecule with drug molecules loaded at terminal surface of branches

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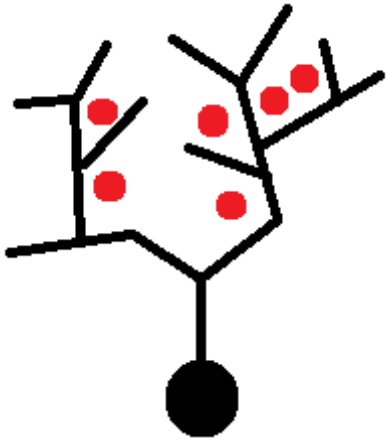

Figure 3: A Dendrimer molecule with drug molecules encapsulated within branches.

There are two types of delivery, one is to a specific type of cell and other as a controlled release from a depot (which may be present in circulation or imbedded in some suitable tissue) [1]. Psividas biosilicon allows drug molecules to be held in nano-sized particles that release a tiny pulse of drug as the biosilicon dissolves. Biosilicon shows resistance to degradation in acid environment[3].

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 [9].

PROPERTIES OF DENDRIMER:

A) Monodispersity- well-defined molecular structure thus workable for a scalable size.

B) Nanoscale size and shape- The small size has a lot of advantages discussed later.

C) Polyvalency- i.e. the functional/reactive groups on the dendrimer structure. This responsible for more interactions between surfaces and bulk materials (adhesives, surface coatings, or polymer cross-linking) [6]. Example: topical vaginal microbicide called Vivagel

D) Adaptive nature of dendrimers: Dendrimers can adapt "native" (e.g. tighter) or "denaturated" (e.g. extended) conformations dependent on the polarity, ionic strength and pH of the solvent [6].

Table 2: Properties of Dendrimer and linear polymers

Sr. 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	Reactivity	High	Low
11	Compressibility	Low	High
12	Polydispersity	Monodisperse	Polydisperse

IDEAL BIOCOMPATIBILITY PROPERTIES:

A) Nontoxic,

B) Non-immunogenic, biopermeable

C) Able to stay in circulation for the time needed to have a clinical effect.

D) Able to target specific structures

ADVANTAGES OF DENDRIMER DRUG DELIVERY:-

A) Medication to the affected part inside a patient's body directly [10].

B) In target drug delivery: Dendrimers are suitable for targeting solid tumours due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumour [1] (enhanced permeation rate). There is also reduction in amount of drug used via targeted delivery (attaching site specific ligands at surface or magnetic guidance) [11] and thus reduction in systemic toxicity

C) Controlled and sustained release of drugs can also be obtained.

D) Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation

E) Bypassing the gastric medium and hence the eschewing the variation due to effect of gastric secretions.

F) Increase in therapeutic efficacy, decrease in side effects: decreased clearance of drug via altered distribution of drug in organs at site of localization and transportation due to controlled and sustained release of the drug[9].

G) Relatively high drug loading.

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H) Preservation of drug activity: as drugs can be incorporated into the systems without any chemical reaction.

I) Limitations of other nanoparticles overcome; for example: overcoming limitations of liposomes like:

1. low encapsulation efficiency
2. rapid leakage of water-soluble drug in presence of blood components
3. Poor storage stability

CHARACTERIZATION OF DENDRITIC POLYMERS

Following methods can be used for characterization of dendritic polymers.

1. **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

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

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

4. **Size exclusion chromatography** (SEC)

5. **Microscopy** like Transmission electron microscopy, Scanning electron microscopy and atomic force microscopy

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

7. **Miscellaneous** like X-ray Photoelectron Spectroscopy (XPS), measurements of dipole moments, titrimetry, etc.

APPLICATIONS OF DENDRIMERS IN DRUG DELIVERY:

A) **Various routes for dendrimer drug delivery:** oral, parenteral, intra-ocular, nasal

B) **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[12].

C) **Dendrimer in ocular drug delivery**- to enhance pilocarpine bioavailability.

D) **Dendrimers in pulmonary drug delivery- for** Enoxaparin (40% increase in relative bioavailability by G2 and G3 generation positively charged PAMAM dendrimers)[6].

E) **Dendrimer in transdermal drug delivery**- improvement in solubility and plasma circulation time. PAMAM dendrimer complex with NSAIDs as permeation enhancers[6].

F) **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 [13].
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).[12, 14, 15]

G) **Dendrimers in targeted drug delivery**- folic acid PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains [6].

H) Dendrimers As Nano-Drugs[12]:
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)[12].

I) **Dendrimers In Photodynamic Therapy [12, 15]:** 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 **(10)**. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

DENDRIMER BASED PRODUCTS [6]:

A) VIVAGEL™ (Starpharma): In clinical phase II trials, it's a topical vaginal microbicide, prevents infection by HIV (polyvalent properties).

B) Stratus® CS Acute Care TM (Dade Behring) - for cardiac diagnostic testing[6].

C) SuperFectTM (Qiagen) - gene transfection agent applicable to a broad range of cell lines

CYTOTOXICITY ISSUES REPORTED IN VIVO [6]:

A) Dendrimers with positively charged surface groups- prone to destabilize cell membranes and cause cell lysis.

B) Generation dependent toxicity-higher generation dendrimers being the most toxic.

C) Degree of substitution, type of amine functionality is important- primary amines being more toxic than secondary or tertiary amines.

CONCLUSION

Dendrimers are promising in solutions against poor solubility, bioavailability, permeability, diagnostic and many other fields of pharmaceutical applications, thus, dendrimers holds a promising future in drug delivery. The risks can be eliminated with proper choice of carrier. Dendrimers, due to its superior architecture; high level of branching, multivalency, globular architecture and molecular weight, prove to be a novel and reliable method of drug delivery. 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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