Dendrimers: A novel carrier for drug delivery system

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ABSTRACT

Dendrimers are macromolecules having highly branched, 3 D structure, nano scale architecture with monodispersity and high functionality. These properties make it attractive candidates as unique and optimum drug carriers for controlled release or targeted delivery. Dendrimer is a smart polymer and as a result of their behavior dendrimers are suitable for a wide range of biomedical and industrial applications and in medical applications such as drug delivery, tumor therapy, diagnostics etc. The field of dendrimers has recently emerged as the most commercially viable technology of this century because of its wide ranging potential applications in many fields such as: healthcare, electronics, photonics, biotechnology, pharmaceuticals, drug delivery, catalysis and nanotechnologies. The review aims mainly on the introduction, objectives, properties, synthesis and applications, in future aspects of dendrimers. Dendrimers help in achieving increased bioavailability, sustained, controlled and targeted release of drug. Thus present review focuses on the fundamentals of dendrimers and their use as drug delivery agents in treatment of disorders.

Dendrimers formulation of delivery is one of the most challenging attractive research areas for pharmaceutical scientists. The use of nonionic or ionic biodegradable polymers in aqueous solutions and colloidal dosage forms such as liposomes, nanoparticles, microspheres, microemulsions, resealed erythrocytes, microcapsules and dendrimers have been studied to overcome the drug delivery problems and improve the site targeting as well as release rate and side effect. Dendrimers as a drug delivery agent is a promising, safe, effective and selective drug delivery option. This review covers a few basic information of dendrimers preparation method and more about their possible application in various areas such as biomedical field, therapeutic agent, diagnostic agent, gene transcription, targeted drug delivery, solubility enhancer, catalyst, additives, printing ink, biomimics and many other areas of science. The dendrimers applications on biomedical field show high progress in future of dendrimers.

Keywords: Dendrimers, Drug Delivery, nanotechnology

INTRODUCTION

The term ‘dendrimer’ originated from Greek word Dendron, meaning tree and meros meaning part. Dendrimers are characterized by its highly branched 3 D structure that provides a high degree of surface functionality and versatility. Dendrimers have a high degree of molecules uniformity, narrow molecular weight distribution, specific size and shape and highly functional terminal surface. Dendrimers have after been referred to as the “polymers of 21st century”. Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle & Coworkers. He synthesized the first ‘cascade molecules’. Dendrimers is mainly act as carrier in solubilization applications, delivery of DNA and oligonucletide, targeting drug at specific receptor site. Dendrimers are being considered as additives in several routes of administration including intravenous, oral, transdermal, pulmonary and ocular. Dendrimers can work as a useful tool for optimizing drug delivery of such problematic drugs with reduced cost of its production and enhance the solubility, bioavailability and permeability. Due to their multivalue and monodisperse character, dendrimers have stimulated wide interest in the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy [1].

Concept of Dendrimers

Dendrimers are built from a starting atom such as nitrogen, to which carbon and other element are added by a repeating series of chemical reaction to

produce a chemical branching structure. Dendrimers become densely packed as they extend out to the periphery, which forms a closed membrane like structure. As the process repeats, successive layers are added and the spheres can be expanded to the size required by the investigator. The result is a spherical macromolecular structure similar to albumin and globulin.

Dendrimers possess distinguished architectural components.

1. An initiator core
2. Interior layers (generations) composed of repeating units radially attached to the interior core.
3. Exterior (terminal functionality) attached to the outermost interior generations.

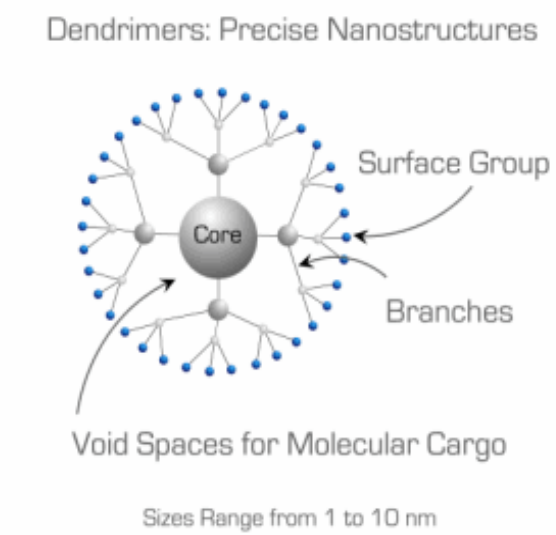

Figure1: Schematic representation of a generation 2 dendrimer [2]

Dendrimers which are lower generation (0, 1 and 2) have highly asymmetric shape and possess more open structure as compared to higher generation dendrimers. As the chain growing the core molecule become larger and more branched (4 and higher generations) dendrimers adopt a globular structure.

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 cant grow because of lack of space. This is called the 'Starburst effect'[3].

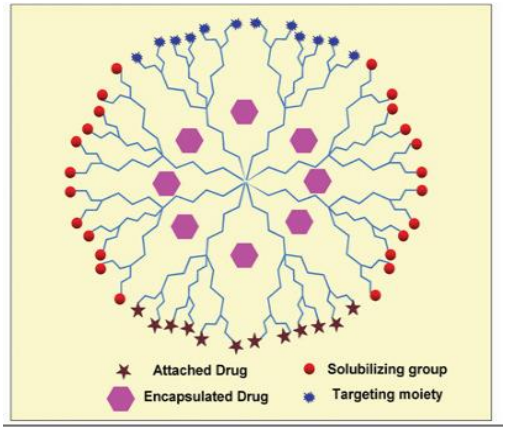

Figure2: Dendritic box encapsulating guest molecules [4]

The purpose of dendrimers is to improve the oral drug delivery because of the oral drug delivery is the most popular and has received more attention in the pharmaceutical field because of ease of production, low cost, conversion of ease of administration and flexibility in designing of dosage. Thus the dendrimeric formulation is possible and effective for the oral drug delivery. Dendrimers provide unique solution to complex delivery problems for ocular drug delivery. The recent problems for ocular drug delivery focus on increasing the residence time of pilocarpine in the eye was overcome by using PAMAM dendrimers with carboxylic and hydroxylic surface groups. These surface modified dendrimers were predicted to enhance pilocarpine bioavailability. So in overall the main objective of the dendrimer formulation is to provide the safe and effective therapy, to overcome the site specific targeting, easy production and low effective cost. Improve the pharmacokinetic and pharmacodynamics properties of a drug so that there is also acceleration in bioavailability [5].

Objectives of Dendrimers formulation

The main objective of the Dendrimer formulation is to improve the efficacy, effectiveness and safety of the drug. Dendrimers have ideal properties which are useful in targeted drug delivery system. One of the most effective cell specific targeting agents delivered by dendrimer is folic acid PAMAM dendrimers modified with carboxy methyl PEG 5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity conferred with the non-PEGylated dendrimer. To

prepare sustained/ Prolong delivery of therapeutic agent in targeted drug delivery system so minimize the patient compliance and decrease of hepatic first pass and chemical degradation in the gastrointestinal tract. Dendrimers are suitable for intravenous /intraperitonial route. This route is the rapidest and simplest method for drug delivery into the systemic circulation. In the oral delivery system of the drug improves patient compliance especially in the patient option. Dendritic polymers are analogous to protein, enzymes and viruses so the good scope of dendrimer in the biomedical fields.

The other objectives of the dendrimer is the diagnostic reagent for tumor imaging by magnetic resonance imaging and as contrast agent, by varying the size hydrophilicity and by combining with tumor targeting antibodies. These compounds can be used for a range of specific imaging purpose [6].

Classification of Dendrimers

1. Radially layered poly (amidoamineorganosilicon) Dendrimers (PAMAMOS) Dr. Petar Dvronic and his colleagues at Michigan Molecular Institute in 1990 discovered this unique first commercial silicon containing dendrimers. This consists of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (os) exteriors.

PAMAM dendrimers are commercially available usually as methanol solutions. Starburst dendrimers is applied as a trademark name for a sub class of PAMAM dendrimers based on a tris- amino ethylene imine core. The name refers to the star like pattern observed when looking at the structure of the high generation dendrimers of this type in two dimensions [7].

2. Poly (amidoamine) dendrimers (PAMAM)

Synthesized by the divergent method, starting from initiator core reagents like ammonia or ethylinediamine. They are commercially available as methanol solutions and ingeneration CD-10 with s different core type and 10 functional surface groups.

3. Poly (Propylene Imine) dendrimers (PPI)

PPI generally having poly-alkyl amines as end groups, and numerous tertiary trispropylene amines present in interior portion and these dendrimers commercially available up to G5, and wide application in material science as well as in biology. PPI dendrimers are available as Astromol [8].

4. Liquid crystalline dendrimers

It is highly branched polymers containing mesogenic groups that can display mesophase behavior. They consist of mesogenic (Liquid crystalline) monomers e.g. mesogen functionalized carbosilicon dendrimers.

5. Chiral dendrimers

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

6. Tectodendrimer

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 [9].

7. Hybrid dendrimers

Hybrid dendrimers are hybrids (block as graft polymers) of dendritic and linear polymers. Hybrid polymers obtained by complete monofunctionalization of the peripheral ammines 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 uni molecular water soluble hyper branched polypropylenes micelles [10].

PROPERTIES OF DENDRIMERS

A. Monodispersity- well defined molecular structure thus workable for a scalable size. Due to their unique synthesis methodology dendrimers can be synthesized with very narrow molecular weight distribution and have a very narrow polydispersity index (PI).

B. Nanoscale size and shape- Dendrimers is globular three-dimensional polymer, their shape largely depends on the generation and number. Shape of dendrimers changes from open hemispherical closes to spherical with increasing generation. Dendrimers with a size range of 1-100 nm. have been synthesized [11].

C. Polyvalency

The functional/reactive groups on the dendrimer structure responsible for more interactions between surfaces and bulk materials (adhesives, surface coating or polymer cross linking) e.g. topical vaginal microbicide called Vivagel.

D. Adaptive nature of dendrimers

Dendrimers can adopt 'native' (e.g. tighter) or 'denaturated' (e.g. extended) conformations dependent on the polarity, ionic strength and p^H of the solvent [12].

METHOD OF PREPARATION

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

First two methods are mainly used for the synthesis of dendrimers [13].

Divergent growth method

This method was introduced by Tomalia. In this method growth of dendrimer originates from a core site. The core is reacted with two or more moles of reagent containing at least two protecting branching sites, follows by removal of the protecting groups, lead to the first generation dendrimers of the described size is obtained. By this approach the first synthesized Dendrimers were polyamidoamine (PAMAM) also known as 'star bust Dendrimers' [14].

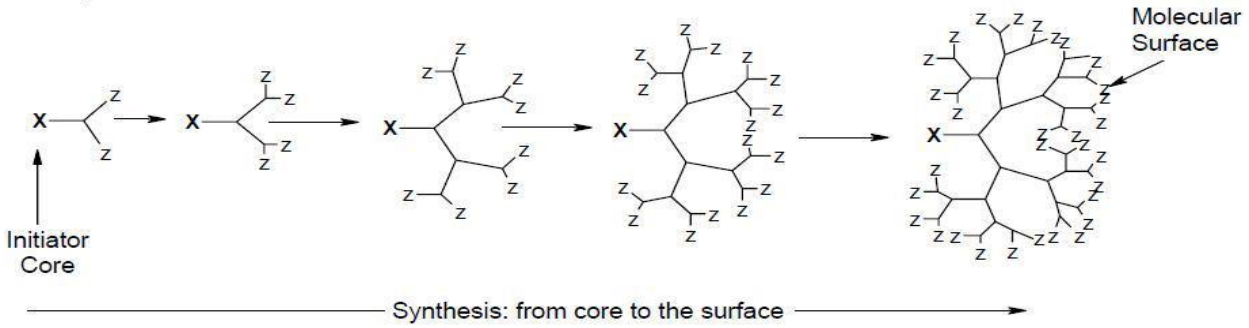

Figure 3: Divergent synthesis of dendrimer [15]

Convergent Dendrimer Growth Method

Divergent method is an 'inward to outward approach whereas convergent approach is 'outward to inward' approach. It starts with synthesis of dendrimer branches separately and then connecting them to the initiator core. The branches are synthesized separately and finally joined to the core to produce dendrimer of desired generation [16].

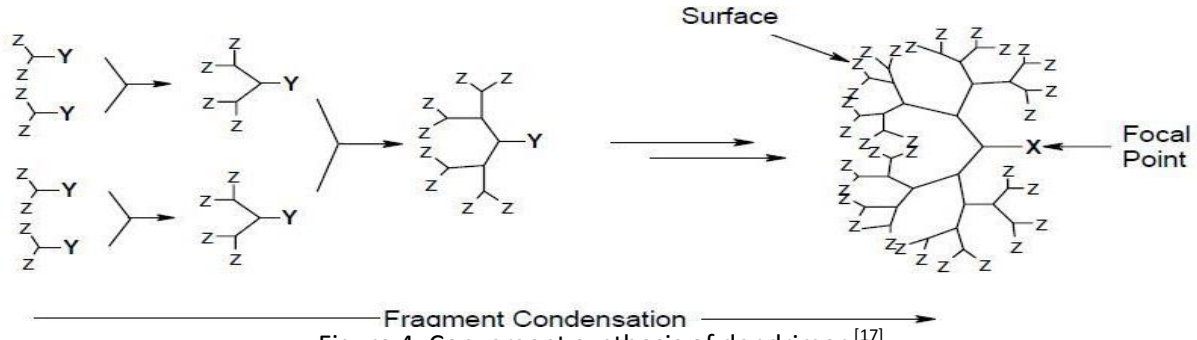

Figure 4: Convergent synthesis of dendrimer [17]

VARIOUS APPLICATIONS OF DENDRIMERS

Dendrimers in Drug Delivery

Dendrimers have attracted attention as possible drug carriers because of their unique properties, their well defined three dimensional structures, the availability of many functional surface groups, their low polydispersity and their ability to mimic biological molecules such as proteins and lipids. Dendrimers have been conjugated to various biologically active molecules such as drugs, antibodies, sugar moieties and lipids. In dendrimer-drug conjugates, the drug is attached through a covalent bond either directly or via a linker/spacer to the surface groups of a dendrimer [18].

Dendrimers in transdermal drug delivery

Dendrimers designed to be highly water soluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulation [19].

Dendrimers in oral drug delivery

Oral drug delivery using the human colon adenocarcinoma cell line, Caco-2, have indicated that low generation PAMAM dendrimers cross cell membranes, Presumable through a combination of two processes i.e. parcellular transport and adsorptive endocytosis.

Dendrimers in ocular drug delivery

Dendrimer provided unique solutions to complex delivery problems for ocular drug delivery. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability [20].

Dendrimers in pulmonary drug delivery

In one of the studies, by measuring plasma anti-factor Xa activity using PAMAM dendrimers in enhancing pulmonary absorption of Enoxoparin. It was observed that G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaporin by 40 % while 62.5 PAMAM half generation containing negative charged groups had no effect.

Dendrimers in targeted drug delivery

Targeted drug delivery is a process of introducing medicine to a patient in a manner that increase the concentration of medication in particular part of body. One of the most effective cell specific targeting agents delivered by dendrimers is folic acid and methotrexate. DNA assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imagining agents so it is easy to develop combinatorial therapeutics [21].

Dendrimers in Antitumor therapy

Dendrimers molecule has found use as diagnostic reagent for tumor imaging by magnetic resonance imaging and as contrast agent by varying the size and hydrophilicity and by combining with tumor targeting antibodies. These compounds can be used for a range of specific imaging purpose. Dendrimers containing photosensitises named 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for photodynamic therapy (PDT) of tumorigenic keratinocytes [22].

Dendrimers in gene delivery

Gene transcription is a direct approach where DNA is coupled to a nanoparticle of inert solid, which is then directly targeted to the cell nucleus. Dendrimer based transcription agents have become routine tools many molecular and cell biologists. Dendrimers are extensively used as non viral vector for gene delivery [23].

Dendrimers for additives, printing inks and paints

Dendrimers can be used in toners material with additives which require less material than these liquid counterparts. Xerox crop, patented a dry toner compound dendrimers as charge enhancing species in the form of an additive. Using additives in printing inks, dendritic polymers ensure uniform adhesion of ink to polar and non polar foils. Dendritic polymers used in polyurethane paints impart surface hardness, scratch resistance, chemical resistance, light fastness, weathering resistance.

Dendrimers as X-ray contrast agents

Number of potential dendritic X-ray contrast agents using various organometallic complexes such as bismuth and tin [24].

MARKETED FORMULATIONS OF DENDRIMER [25]

Product	Manufacture	Application
Vivagel	Star pharma	Vaginal gel for

		preventing HIV
Strauts CS	Dade Behring	Cardiac marker
Superfect	Qiagen	Gene transfection
Alert Ticket	US army research laboratory	Anthrax Detection

FUTURE PROSPECTS

An additional area of research that is currently being explored is the development of dendrimers clusters, where several dendrimers are bound together through physical or chemical forces to assemble a multifunctional therapeutic system that incorporates the anticancer drugs, targeting ligands, and imaging agents, which will create new way for combination anticancer therapy along with *in vivo* imaging of the targeted tumor. Despite the effectiveness of dendrimers based drug delivery systems, their application in cancer therapies with defined dosage regimen is still not acceptable, which can be due to the difficulty of synthesizing the desired systems in large quantities at clinical grade purity for clinical trials coupled with regulatory hurdles that demand detailed characterization of the polymeric carriers along with the linkages and the incorporated drug.

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 dendrimers holds a promising future in various pharmaceutical applications and diagnostic field in the coming years as they posses unique properties such as high degree of branching, multi valency, globular architecture and well defined molecular weight, there by offering scaffold for drug delivery. Recent success in simplifying and optimizing the synthesis of dendrimers provide a large variety of structures with reduced cost of their production. Also, as a research progress, newer applications of dendrimers will emerge and they would witness an increasing number of commercialized dendrimer based drug delivery.

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