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DENDRIMER APPLICATIONS – A REVIEW

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ABSTRACT

As a new class of a synthetic polymers based on a well-defined cascade macromolecules synthesized to reach various demands in the field of electrical, chemical, biological, medicinal and biotechnology. Dendrimers have proved themselves to be very challenging and applicative; as the structure provides high degree of surface functionality, versatility and the unique properties like uniform size, high degree of branching, multivalency, water solubility, well defined molecular weight and also the available internal cavities. The ability of this macromolecule to construct a definite architectural design of dendrimers with respect to size and shape, length of branching, density, and its well defined molecular structure and segmented spherical construction has opened a wide area of research by understanding the interactions taking place between the biological entities. This review cover a few basic information of dendrimers and much about their possible applications in various areas such as biomedical field, as imaging contrast agents, therapeutic agent, diagnostic agent, gene transfection, drug delivery, targeted drug delivery, solubility enhancer, light harvesting, catalyst, additives, printing ink, paints, biomimics, and many other areas of science. The impact of dendrimer applications on biomedical field as demonstrated in this review; shows major potential and high hopes for the future of dendrimers.

KEYWORDS: Dendrimer, Drug carriers, PAMAM, Dendritic polymers.

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1. INTRODUCTION

The dendritic polymer includes both dendrimers and hyper branched polymer. The term dendrimer is originated from the Greek word [1] 'Dendron' which means tree like and 'meros' which means parts or unit. Dendrimers are tree like in structure and appearance. It has a three dimensional structural symmetry. A large number of branches during polymer synthesis lead to formation of macromolecule with many end groups. Out of highly branched polymers, dendrimers are perfectly branched uniform structure and hyper branched polymers are randomly branched [2]. A generally accepted definition of dendrimer is a monodisperse macromolecule with perfectly branched regular structure and having at least one branched junction at each repeat unit [3]. However it is difficult to place, dendritic polymers, especially Dendron's and dendrimers, definitely in any branch of chemistry. They are sometimes described in terms of supramolecular chemistry or polymer chemistry, although in some cases they are neither supramolecule nor polymer in reality. However they are treated as macromolecules. A structurally perfect dendrimer has monodispersity, defined molecular size, and defined number of end groups. Nanoarchitecture[4] with shell structure, structural precision, hydrophilic or lypophilic balance by design, accessible molecular surface and good flexibility; which offers researchers possibility to work in that particular area. Using distinct properties of the dendrimer in architecture; photo physical, photochemical, electrochemical or catalytic functions at the core of dendrimers have placed active sites for researchers. Present review will have more focus on recent studies and many important applications of dendrimers in various fields of science.

2. *APPPLICATIONS OF DENDRIMERS*

Dendrimer possess its unique structural features like nanoscopic size, spheroidal surface, high branching, cavernous interior, etc. and exciting properties, like low viscosity, high solubility, high reactivity, in combination with the high functionalities of the dendritic polymers suggested that they have wide number of potential applications in different fields [4]. These included medicinal and diagnosis applications[5, 6], gene therapy and chemical sensors [7, 8], drug delivery system[9-11], adhesive and coatings[12], light harvesting material[13], catalyst[14, 15], electronic applications[16], separating agents[17], and many more[18, 19].

2.1 Dendrimers in biomedical field

The dendritic polymer has advantage in biomedical applications. These dendritic polymers are analogous to protein, enzymes and viruses and easily functionalized. Dendrimers and other molecules can either be attached to periphery or can be encapsulated in their interior voids. The dendrimer should possess certain qualities for its utility as biological agents. The dendrimer should be non toxic, non immunogenic, bio permeable, able to target specific structure. Due to specific synthesis, Polyamidoamine (PAMAM) dendrimers possess the interesting properties, which distinguish it from classical linear polymers and are the most studied starburst macromolecule. PAMAM dendrimers can also be used to target tumour cells. Targeting groups can be conjugated to the host dendrimers surface [20] to allow the imaging agent to bond selectively to specific site such as receptors on tumour cell to improve detection. Cisplatin was complexed to the surface groups of a carboxylate-terminated PAMAM dendrimer which led to a tenfold increase in the solubility of cisplatin compared to the free drug [40]. It was also found that the use of lower molecular weight dendrimers with denser interiors and ellipsoidal, flattered or elongated shaped may result in improved dendritic MRI contrast agents.

2.2 Dendrimer as magnetic resonance imaging contrast agents

Dendrimer based metal chelates act as a magnetic resonance imaging contrast agent. Dendrimers are highly suited and used as image contrast media because of their properties. Many tests carried on dendrimers

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have shown that dendrimers are stronger contrast agent than conventional ones. They can improve visualisation of vascular structure in magnetic resonance angiography (MRA) of the body. Moreover, the sixth generation polygadolinium dendrimer displayed a prolonged enhancement with a half-life of 200 min compared to 24 min for monovalent gadolinium agent. This prolonged enhancement time is extremely useful for3D time-of-flight MR angiography [21]. In the recent study, it was found that the molecular size of a dendrimer-based MRI agent altered the route of excretion. Contrast agents having molecular weight less than 60 kDa were excreted through kidney being potentially suitable as functional renal contrast agents. Larger sized and hydrophilic contrast agents were found better for use as blood pool contrast agent. Larger hydrophilic agents were useful for lymphatic imaging. Finally, these dendrimer based MRI agents were recognised by the pharmaceutical industry which results in various commercial developments.

2.3 Dendrimers in Antitumor Therapy

Dendrimers molecule has found use as diagnostic reagent for tumour imaging by magnetic resonance imaging and as contrast agent; by varying the size and hydrophilicity and by combining with tumour targeting antibodies, these compounds can be used for a range of specific imaging purpose [22] The drug used should be non-toxic, under non-irradiative condition, thus acting as prodrug when not irradiated. 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 [23]. The administration of a light activated photosensitizing drug that selectively concentrates in diseased tissue were involved in cancer treatment. Also, glycodendrimer constitute an important class of therapeutic molecules. The dendrimers were investigated with the purpose of producing a drug that would interact with carcinoma derived T-antigen-binding receptors to interfere with carcinoma growth. This type of Glycodendrimer reacted in a generation dependent way with monoclonal antibodies against the T-antigen with higher generation having higher affinities. The therapeutic uses of dendrimers may be within the cancer field where numerous examples of targeting tumours for diagnostic purpose have been described and where it is possible to define a cancer specific cell surface component that can be targeted.

2.4 Dendrimers as Gene Transfer Reagents

Gene transfection is a direct approach where DNA is coupled to a nanoparticle of inert solid, which is then directly targeted to the cell nucleus. As transfection, if eukaryotic cells is a methodology for effective changes in the genetic material of cells [24]. It has become much valuable tool in molecular biology for studying mutations and regulation processes of genes or inducing over expression of desired proteins. The ideal vector for transfection should be apart from high efficiency, non-immunogenic, non-toxic, either bio-degradable or excretable and has long blood circulation time. The use of dendrimers for transfection was first reported by the group of Szoka [25] and Baker [26]. PAMAM dendrimers were the first found to be useful for transfection. The company named Quiagen developed a commercial transfection system based on PAMAM dendrimers followed by the work of Szoda et al and Baker et al [27]. Dendrimers are actively under investigation for the delivery of DNA and small organic molecule drugs, especially for cancer therapy. 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 [28-38]. It was also known that, the dendrimers of high structural flexibility and partially degraded high generation dendrimers are better suited for certain gene delivery operations. The delivery of therapeutic nucleic acids, normally in the form of plasmids, but increasingly also as smaller oligomers remains one of the major obstacles currently hampering the further exploitation of genetic therapies. The suitability of any gene delivery system will always have to be matched with the clinical situation, the specific disease and chosen therapeutic strategy. Furthermore, a series of amphiphilic dendrimers based on the rigid diphenylethyne core was synthesized and their activities as transfection agent were

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described [39]. These dendrimers show high transfection activity, variety of substitution patterns, but the hydrophobic parameters influenced the DNA binding and transport more strongly than predicted, exhibits lower toxicity and an unusual serum effect. These dendrimers do not show a minimum size limitation for transfection. However, an optimum molecular weight greater than 116kDa was found for PAMAM dendrimers which gave an optimum activity. In one of the study, dendritic amidoamine side chains of different generations were covalently attached to the chitosan which was chosen to combine the biological activities of chitosan in gene delivery, antibacterial activity and wound healing activity with the delivery benefits found for dendrimers [39].

2.5 Dendrimers in targeted drug delivery

Targeted drug delivery is a process of introducing medicine to a patient in a manner that increases the concentration of medication in particular part of body. A certain amount of therapeutic agent is delivered for a prolonged period of time to the targeted diseased area within the body, which helps to maintain the required plasma and tissue drug level in the body. Dendrimers have multifunctionality and high potential for drug delivery applications as they possess high density and wide variety of functional groups on its surface [9-11]. Its well defined molecular structure, segmental spherical construction of dendrimers offers an interesting architecture for dendrimers. If one of these segments is attached with active drug molecule, the other can be highlighted as targeting group. Due to this double functional group, the plasma level of the drugs will stay at desired level for longer time period and increase its Pharmaceutical efficiency. Generally, the therapeutic efficiency of drug is diminished due to low bioavailability, insolubility, toxicity and the decomposition of drug under biological circumstances[6]. Using Dendrimers containing targeting moieties onto conjugated drug molecule, the above shortcomings can be overcome.

2.6 Dendrimers in drug delivery

Drug molecule can be loaded in the interior and also to the surface of dendrimers. Encapsulation of the well-known anticancer drug cisplatin within PAMAM dendrimers gave conjugates which can slow down release and higher accumulation in solid tumours and it has low toxicity than free cisplatin [40]. The encapsulation of silver salts within PAMAM dendrimers produces conjugates that can exhibit slow silver release rates along with antimicrobial activities against different gram positive bacteria [41, 42]. Dendrimers are highly soluble and compatible, due to which, solubility of drug in body can be increased. As dendrimers is water soluble and capable of binding and solubilising acidic hydrophobic molecules with antifungal and antibacterial properties. Drug molecules can be incorporated into dendrimers via either complexation or encapsulation[43].Therapeutic agents can be attached to a dendrimer to direct the delivery. For example, dendrimers in boron neutron capture therapy (BNCT) Vol.48 Dendrimers 205.

2.7 Dendrimers in transdermal drug delivery

Transdermal drug delivery has come into existence long back. To improve the effectiveness of the drug transdermal drug delivery system was emerged. Drug delivery through skin to achieve a systematic effect of drug is known as transdermal drug delivery. Transdermal delivery provides controlled, constant administration of the drug which extends the activity of drug having short half-life through the reservoir of drug present in the delivery system and its controlled release characteristics.[44] The drug which is to be delivered should have low melting point, should be potent, having short half life and non- irritating. PAMAM dendrimer complex with Non Steroidal Anti-inflammatory Drugs (e.g. Ketoprofen, Diflunisal) which are very effective in treatment of acute and chronic rheumatoid and osteoarthritis, could be improving the drug permeation through the skin as penetration enhancers [45]. The model drugs Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies.

2.8 Dendrimers in oral drug delivery

Oral drug delivery is the most popular and has received more attention in the pharmaceutical field because of ease of production, low cost, convenience of ease of administration and flexibility in designing of dosage. The oral drug delivery depends on various factors such as type of delivery system, the disease being treated, and the patient, the length of the therapy and properties of the drug. The controlled release system for the oral use are mostly solids and based on dissolution, diffusion or a combination of both mechanisms in the control of release rate of drug [44]. One important advantage of oral drug delivery is less fluctuating plasma drug level is maintained with controlled drug delivery systems, because the drug is slowly released from the dosage continuously and maintains the constant blood level. Along with the merits there are some demerits of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes [46]. D'Emanuele and his research group [47] investigated effect of dendrimer generation and conjugation on the cytotoxicity, permeation and transport mechanism of PAMAM dendrimer. As the concentration and generation increased, the increase in cytotoxicity and permeation of dendrimers resulted. While reduction in cytotoxicity was observed by conjugation with lauryl chloride.

2.9 Dendrimers in ocular drug delivery:

The topical application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery. An ideal ocular drug-delivery system should be non-irritating, biocompatible, sterile, isotonic and biodegradable [48]. 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 or hydroxyl surface groups. These surface modified dendrimers were predicted to enhance pilocarpine bioavailability [49].

2.10 Dendrimers in pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery also [50]. In one of the studies, by measuring plasma anti-factor Xa activity using PAMAM dendrimers in enhancing pulmonary absorption of Enoxaparin, and by observing prevention efficacy of deep vein thrombosis in a rodent model, it was observed that G2and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40% while G2.5 PAMAM half generation dendrimers containing negatively charged carboxylic groups had no effect. So the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery [50].

2.11 Dendrimers used for enhancing the solubility

PAMAM dendrimers are expected to have potential applications in enhancing the solubility for drug delivery systems [1, 2]. Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micelle nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour [51]. Dendrimers that are soluble in water are capable of binding and solubilising small acidic hydrophobic molecule with antifungal or antibacterial activities. Dendrimer possess unimolecular micelle and do not possess a critical micelle concentration. These characteristic offers the opportunity to soluble poorly soluble drugs by encapsulating them within the dendritic structure [51]. Dendrimer based carriers' offers the opportunity to enhance the oral bioavailability of problematic drugs. Thus, dendrimer nanocarriers offer the potential to enhance the bioavailability of drugs that are poorly soluble and/or substrates for efflux transporters.

2.12 Dendrimers for additives, printing inks and paints

Dendrimers can be used in toners material with additives which require less material than their liquid counterparts. Xerox Corp. Patented a dry toner compound dendrimers as charge enhancing species in the form of an additive [52]. Using additives in printing inks, dendritic polymers ensure uniform adhesion of ink to polar and non-polar foils. Here, first the hyper branched compounds attach themselves to the pigment particles and there are still large numbers of functional groups remaining to give adhesion to the surface of the foils. Dendritic polymers used in polyurethane

paints impart surface hardness, scratch resistance, chemical resistance, light fastness, weathering resistance as well as high gloss, because of which they are used in furniture and automotive industries.
Use of Dendrimer additives in the composition of the invention is effective for altering the surface characterization of thermo plastic resin after moulding. One of example for this is polycarbonates, which are widely used as an engineering thermoplastic for providing a unique combination of toughness, stiffness, high softening temperature and processibility.

2.13 Dendrimers in light harvesting material

A significant research has been of interest for designing molecules with controlled motion of charges. The use of Dendrimers is because of its multiple functionality and structural features. Moving from the periphery to the core, the functional groups decreases; which render dendrimers in light harvesting. Most of the literature report shows direction towards energy funnelling from the chromophore in the periphery to another chromophore at the core [53]. A study on π-conjugated dendrimers family based on truxene and thienylethynylene were synthesised. These synthesised dendrimers show intrinsic energy gradient from periphery to the core along with broad absorption in the UV-ris range and proficient energy transfer to the lower energy centre. Hence, they are highly potential as light harvesting materials.

2.14 Dendrimers as Catalyst

Dendritic polymers have been used in large amount as catalyst. There are two major reasons for the advantage of using dendritic polymers. One of the reasons is possibility of creating a large dendrimer with many active sites. These types of catalyst are an intermediate between heterogeneous and homogeneous catalyst which can be separated easily by filtration [54]. The second important reason is, there is possibility of encapsulating a single catalytic site whose activities can be enhanced by dendritic superstructure [55]. Dendrimers have multifunctional surface with active catalytic site. Insoluble materials can be encapsulated such as metals, and transport them into a solvent in interior of dendrimer. Cooper and co-workers [56] synthesized fluorinated dendrimers which are soluble in supercritical CO_2 and can be used to extract strongly hydrophilic compounds from water into liquid CO_2.

2.15 Dendrimers as Biomimics

Dendrimers having their well defined macromolecular dimensions and compartmentalised structure are ideal mimics for a wide variety of biomolecules. The commercially available dendrimers provide possibility to create micro environments. PAMAM dendrimers with their network consisting of numerous mixed tertiary amines. Dendrimers have ability to expose the multivalent surface for increased binding of biomolecules. Also, dendrimers have ability to create a micro environment inside the dendrimer, which makes artificial catalytic sites or cavities possessing different properties for construction of enzyme mimics. Dendrimer molecules are characterized by zones of different density, depending upon the rigidity or the conformational mobility of their scaffold; they combine dense and less dense areas. They are flexible and have cavities to accommodate solvent to act as host compounds for guest substance. By using dendrimers more favourable qualities compared to naturally occurring proteins can be obtained. More densely packed structure compared to the natural proteins, for example certain peptide based dendrimer system show a significant increased resistance towards proteases [57]. The dendrimer is also used as a building block to mimic a non-globular collagen structure, showing that dendrimers, although being mostly globular shaped, may be used as mimics of non-globular structures. Dendrimers may also mimic numerous protein –based receptors utilised in nature for specific biological recognition.Glycomometics are synthesized analogous carbohydrate whose structure has been simplified and modified, and is an active ingredient, which can be used for treatment of chronic inflammatory ailment such as rheumatism,dermatitisand soriasis.(According to Diederich et al) Dendritic porphyrin-metal complexes consist of flexible dendritic poly (ether amide) units [58]. Study of first and second generations of this dendrimer revealed that the reduction potential is shifted towards positive values, than sufficient shielding is obtained.

2.16 Dendrimers as a separating agent

A study of variety of compounds synthesized to determine suitability for enhancing boron rejection by reverse osmosis and nanofilteration membrane to separate born from sea water has been developed. For separation, compound must have amphiphile chemical__structure and form micelle in aqueous solution. As a new compound dendrimers with a high density of functional moiety, is able to form micelle structure which can be easily separated and recovered by ultra filtration membrane. These micelles provide high functional density at the surface of the particle, high surface area and ease of separation for isolation and regeneration of the compound. It was found that unmodified commercial dendrimeric compounds containing amine and hydroxyl groups are generally more effective for boron absorption.

Polyamidoamine (PAMAM) dendrimers are used as chelating agents for the removal of certain metal ions from waste water [59] and from contaminated soil [60].Other modified chelating PAMAM and poly (propyleneimine) dendrimer are also reported to be good ligands for a various hard metal cations [61, 62], or can be described as “nanosponges” for the removal of Polycyclic aromatic hydrocarbons [63] and other particles [64].

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