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DENDRIMERS AND ITS APPLICATION: A REVIEW

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ABSTRACT
A dendrimer is typically described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and adaptability. Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. The structure of those materials features a great impact on their physical and chemical properties. As a results of their unique behaviour dendrimers are suitable for a good range of biomedical and industrial applications. The paper gives a concise review of dendrimers" physico-chemical properties and their possible use in various areas of research, technology and treatment. The bioactive agents can be easily encapsulated into the interior of the dendrimers or chemically attached that is conjugated or physically adsorbed onto the dendrimer surface, serving the desired properties of the carrier to the precise needs of the active material and its therapeutic applications. The review aims to stress on construction, characterisation, drug delivery and possible application of dendrimers in various areas of research, technology and treatment.

KEYWORDS: Dendrimer, drug delivery, polyamidoamine dendrimer (PAMAM).

INTRODUCTION
Dendrimers are repeatedly branched molecules. The huge number of papers on dendritic architectures like dendrimers, dendronized, hyperbranched and brushpolymers has generated a huge sort of inconsistent terms and definitions making a transparent and concise unfolding of this topic highly difficult. A dendrimer is usually described as a macromolecule, which is characterized by its highly branched three diamentional structure that gives a high degree of surface functionality and flexibility. Dendrimers have often been mentioned because the "Polymers of the 21st century". Dendrimer chemistry was first introduced in 1978 by Fritz Vogtle and coworkers. He synthesized the first "cascade molecules". In 1985, Donald A. Tomalia, synthesized the first family of dendrimers. The word "dendrimer" originated from two words, the Greek word dendron, meaning tree, and meros, meaning part. At the same time, Newkome et al independently reported synthesis of similar macromolecules. They called them 'arborols' from the Latin word 'arbor' also meaning a tree. The term cascade molecule is additionally used, but 'dendrimer' is that the best established one. Due to their multivalent and monodisperse character, dendrimers have stimulated wide interest within the field of chemistry and biology, especially in applications like drug delivery, gene therapy and chemotherapy. Dendrimers then experienced an explosion of scientific interest due to their unique molecular architecture. Dendrimer is nano sized radially symmetric molecules with well defined, homogeneous and monodisperse structure consisting of tree like arms or branches. (Kukowska-Latallo JF,et.al., 1996) Dendrimer can be prepared with regularity and controlled molecular weight and the macromolecules consist of a polyfunctional central core covalently linked to layer of repeating units [generations] and a no. of terminal groups. (Pushkar, S., et. al., 2006) Surface groups of Dendrimers can be neutral, or positively/negatively charged. Poly [amidoamine] [PAMAM] Dendrimers is the first and most extensively studied family of Dendrimers for biomedical use. (Daniel Q. McNerny, et. al., 2010) Dendrimers can enhance the toxicity of a material by increasing the local concentration of a therapeutic via multivalent interactions with surface-bound ligands and by enhancing retention within the targeted tissue. (Jevprasesphant R, et. al., 2003) In broad-spectrum, cationic dendrimers have been revealed to display nonspecific toxicities and must be customized to stop accumulation in the liver. (Jain N.K., et. al., 2010 & Sivabalan M., et. al., 2013) The differences in toxicities among cationic and anionic dendrimers have also been confirmed in vivo. (Malik N., 2000) Using a zebra fish embryo model, carboxyl terminated dendrimer was significantly less toxic than G4 amine-terminated dendrimer further considerate the toxicity of cationic dendrimers is critical for successful use in gene transfection applications. (Tatiana Tocchini Felippotti,

et. al., 2011) Where a positively charged surface is required for ionic complexation with DNA and to act as a proton buffer, leading to endosome disruption. (Tomalia D. A., et. al., 1990) These polymers are unique, spherical molecules, whose molecular construction consists of a core and repeat units with branching and terminal groups. Each repeating unit contains branching point to which two or several new repeating units are attached. (Antonio Quintana, et. al., 2002) Polyamidoamine [PAMAM] dendrimer are highly branched macromolecules with well defined architecture that can serve as a unique platform for a variety of therapeutic agents. (Frechet J.M.J., 2001)

CHARACTERISTIC OF DENDRIMERS

Architecture: Dendrimers shows improved physical and chemical properties due to their molecular architecture. The dendrimers shape depend on the generation i.e. lower generation shows open planar elliptical shape while, higher generation shows compact-spherical shape [Barabara, K. and B. Maria, 2001]

Solubility: Surface groups of the dendrimers plays an important role in the solubility of dendrimers. If the surface end groups are hydrophobic in nature, then dendrimers are soluble in nonpolar solvent. If the surface end groups are hydrophilic in nature and dendrimers are soluble in polar solvent. The high solubility, miscibility and reactivity and binding capacity of dendrimers is due to the presence of many chain end groups. (Barabara, K. and B. Maria, 2001)

Monodispersity: Dendrimers are monodisperse in nature i.e. they have an isomolecular class, their molecular size; shape and character of organic moieties are attuned and controlled.

Viscosity: In solution dendrimers form a strongly crowded ball which influences its rheological properties. The intrinsic viscosity dendrimers solution does not show linear connection with mass but it is highest for a specific generation and then it begins to decrease. (Tolia G.T., et. al., 2008).

PROPERTIES OF DENDRIMER

Properties of dendrimer and linear compact

S.n.	Property	Dendrimer	Linear polymer
1.	Structure	Compact, Globular	Not compact
2.	Synthesis	Careful & stepwise growth	Single steppolycondensation
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.	Aq. solubility	High	Low
8.	Non-polar solubility	High	Low
9.	Viscosity	Non-linear relationship with molecular weight	Linear relation with molecular weight
10.	Polydispersity	Monodisperse	Polydisperse

APPLICATION OF DENDRIMER

Dendrimers as Cellular Drug Delivery Carrier

Pure drug [Ibuprofen] enters into the cell in 3 hours except the dendrimers ibuprofen complexes entered into the cell in 1 hour. So these result shows that dendrimers can carry the complex drug efficiently inside the cell. (Antonio Quintana, et.al., 2002).

Dendrimers as Solubility Enhancer

Dendrimers are unimolecular micellar in nature because these have both stability. Hydrophobic and hydrophilic layer. Hydrophilic layerforms the core and hydrophilic layer forms the outer surface. Dendrimers do not have a critical micelle concentration. Due to these properties dendrimers enhance the solubility of poorly soluble drug by forming covalent, non-covalent complexes with drug molecules molecular and hydrophobes. (Hawaker, C., 1993 & Sadekar S. and Ghandehari H., 2012).

CNS delivery

Dendrimers, are regularly branched polymer molecules with branches growing from one or several centers. They can be formulated noncovalently with biological agents, such as DNA or conjugated with pro-drug or imaging agents and thus can be used as delivery vehicles for drug therapy or molecular imaging. To the best of our knowledge dendrimers have not been evaluated so far for CNS delivery except for few studies on intratumoral delivery of dendrimer conjugates with anticancer agents to treat glioma. Notably, the generation and surface properties of dendrimers were found to be very important.

Dendrimers in ocular drug delivery

The topical application of pharmaceutical active drugs to the eye is the most arranged route of administration for the management of various ocular disorders. Dendrimers supply unique solutions to complex delivery trouble for ocular drug delivery. An ideal ocular drug delivery

system should be non-irritating, biocompatible, sterile, isotonic and biodegradable (Tatiana Tocchini Felippotti, et. al., 1990). The recent problems for ocular drug delivery focus on increasing the residence time of pilocarpine in the ocular delivery was overcome by using PAMAM dendrimers with Carboxylic or hydroxyl surface groups. These surface modified dendrimers were predicted to Enhance pilocarpine bioavailability. (Nanjwade B.K., 2011).

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 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 mainly solids and based on dissolution, diffusion or a mixture of both mechanisms in the control of release rate of drug. (Keerti Jain, et. al., 2010).

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. (I.B. Erick, 2006).

Dendrimers in Targeted and Controlled Release Drug Delivery

The dendrimers facilitate the passive targeting of drug to solid tumours. This is due to their enhanced solubility and plasma circulation time. EPR [Enhanced Permeation and Retention] in tumour tissues leads to reduce cytotoxicity of anticancer drug and increased uptake by cancer cell lines. Example- Doxorubicin. (Tomalia D.A., 2005) Nanoshells [encrusted colloids with a non-conducting nanoparticle core enclosed by a thin metal shell] and nanorods [e.g., copolymers, gold] are used in combination with specific wavelengths of lights and heat technology for cancer therapy. (Patel V., et. al., 2012).

Dendrimers in Gene Delivery

Dendrimers can be use as a carrier in gene therapy. Example- PAMAM dendrimers have terminal amino groups which interact with phosphate group of nucleic acid. So PAMAM dendrimers improved physical and chemical properties. These have been tested as a genetic material vector. (Sonke S, Tomalia D.A., 2005) Super Fect TM is a transfection reagent, it consist of activated dendrimers Activated dendrimers can carry a large amount of genetic material than viruses Super Fect-DNA complex are highly stable and have high transfection efficiency is due to their well defined shape and low pk of the amines. Polycationic polymers [e.g., SuperFect® dendrimers, poly-[l-lysine]] as synthetic non-viral vectors with decrease cytotoxicity. (Barabara, K. and B. Maria, 2001).

Dendrimers based product in cosmetics

Dendrimers have a great contribution on cosmetics. Several cosmetics industry [amidoamine] dendrimers as ophthalmic vehicle used dendrimers in the formulation. L'Oreal has a patent for using dendrimers in the production of cosmetics like mascara or nail polish. Unilever also have a patent for dendrimers in the production of formulation for used in spray, gels and lotions. (Sonke S, Tomalia D.A., 2005 & Jaeschke H. Gores, 2002).

Dendrimers in Waste Water Treatment

Dendritic polymers are used in the purification of water contaminated by toxic metal ion, inorganic solute and organic solutes. (Kukowska-Latallo J.F., et. al., 1996).

Dendrimers in pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery also. 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 completely charged PAMAM dendrimers amplified the virtual bioavailability of Enoxaparin by 40% while G2.5 PAMAM half generation dendrimers contain negatively charged carboxylic groups and had no effect. Thus the positively charged dendrimers are appropriate carrier for Enoxaparin pulmonary delivery.

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. (Jaeschke H. Gores, et. al., 2002) 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 helpful in management of acute and chronic rheumatoid and osteoarthritis, could be recovering the drug penetration through the skin as dispersion enhancers. (Csaba N, et. al., 2006). the model drugs Ketoprofen and Diflunisal were combined with G5 PAMAM dendrimer and investigate for different studies.

Dendritic micelles

Dendrimers, the highly branched monodisperse macromolecules, have a large number of tunable surface groups and an interior that provides space as well as microenvironment suitable for host-guest chemistry.

(Zheng F, Zimmerman SC. 1997, Mark H.F. 2004) Dendritic micelles are generally unimolecular and do not suffer from even the low CMC that the linear polymer based micelles have. Also, these have been shown to be rapidly internalized into cells through endocytosis due to their nanometerscale dimensions. By virtue of these unique features, dendrimers are being recently studied for applications in gene therapy and as drug carriers and as contrast agents in imaging (Patri AK, Majoros IJ, Baker JR. 2002, Bosman A.W., Janssen H.M., Meijer E.W. 1999). It is evident from the above discussion that dendritic micelles with anionic or PEG groups on the periphery are promising carriers for drug delivery. Further, functionalized biocompatible dendrimers will be attractive for multiple dendrimer-drug conjugates. It will be interesting not only to have highly functionalized dendrimers but also to direct the functionalities towards the concave interior of the dendrimer for better encapsulation of the drug.

Dendrimer-based nanoparticles for lung delivery

Kukowska-Latallo et al investigated the ability of PAMAM dendrimers to augment plasmid DNA gene transfer in-vivo and evaluates the targeting of the lung by alternative routes of administration (Kukowska-Latallo JF, Raczka E, 2000). They suggested that vascular administration seemed to achieve expression in the lung parenchyma, mainly within the alveoli, while endobronchial administration primarily targeted bronchial epithelium, indicating that each delivery route requires different vectors to achieve optimal trans-gene expression that each approach appears to target different cells within the lung. Rudolph et al compared the properties of branched polyethylenimine (PEI) 25 kDa and fractured PAMAM dendrimers for topical gene transfer to the airways in-vivo (Rudolph C, Lausier J, 2000). Bai et al produced low molecular weight heparin (LMWH)–dendrimer complex through electrostatic interactions using various PAMAM dendrimers then evaluated both the safety and the efficacy of the drug–dendrimer formulations in preventing deep vein thrombosis in-vivo and in-situ (Bai S, Thomas C, Ahsan F. 2007). They concluded that cationic dendrimers can be used as pulmonary delivery carriers for a relatively large molecular weight anionic drug. These carriers bind anionic drug molecules most likely via electrostatic interactions and increase drug absorption through charge neutralization.

Dendritic catalysts / enzymes

The combination of high surface area and high solubility makes dendrimers useful as nanoscale catalysts. Dendrimers have a multifunctional surface and all catalytic sites are always exposed towards the reaction mixture. They can be recovered from the reaction mixture by easy ultra filtration methods (Frechet JMJ, Donald A. 2002). Dendritic shells can be used to create a microenvironment favorable for catalysis or provide shielding for functional groups at the dendritic core. Because of their ‘pseudo’-spherical nature and their resultant conformations the metal sites in these welldefined polymeric catalysts should be easily accessible for substrate molecules and reagents, and therefore exhibit characteristicsfast kinetics, specificity and solubility (Kofoed J, Reymond J. 2005). Metallodendritic catalysts, catalysis with phosphine-based dendrimers, catalysis with (metallo) dendrimers containing chiral ligands, non-metal containing dendrimers are some of the examples of dendritic catalysts and enzymes.

CONCLUSION

The high level of control over the architecture of dendrimers, their size, shape, branching length and density, and their surface functionality, makes these compounds ideal carriers in biomedical application such as drug delivery, gene transfection and imaging. Despite two decades since the discovery of dendrimers the multi-step synthesis still requires great effort. Unless there is a significant breakthrough in this field, only few applications for which the unique dendrimer structure is crucial will pass the cost-benefit test.

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