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DENDRIMERS: MULTIFUNCTIONAL DRUG DELIVERY CARRIERS

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Abstract: Nano Technology is one of the most widely used concept in the field of drug delivery and therapeutics in modern day pharmaceutics. Dendrimers are a class of nano materials which has been found particularly useful in the drug delivery. Even though dendrimer technology is in its infancy it offers many attractive features which makes them desirable to be used as novel carriers. Dendrimers, also referred as modern day polymers, they offer much more good properties than the conventional polymers. There are different types of dendrimers to be used for different purposes. Due to their unique architecture these have improved physical and chemical properties. Due to their terminal groups these show high solubility, miscibility and reactivity. Dendrimers have well defined size, shape, molecular weight and mono dispersity. These properties make the dendrimers a suitable carrier in drug delivery application. This review summarizes the possible applications of the dendrimers in the field of drug delivery, shows their advantage over conventional linear polymers and shows the need to study the dendrimers.

I. INTRODUCTION

Dendrimers are nano-sized, radially symmetric molecules with well-defined, homogeneous, and monodisperse structure consisting of tree-like arms or branches [1].These hyper branched macromolecules were first discovered by Fritz Vogtle in 1978, by Donald Tomalia and co-workers in the early 1980s, and at the same time, but independently by George R. Newkome. The term dendrimers originates from the two Greek words dendron and meros (Dendron – tree, Meros – part). Newkome's group called them as arborols from a Latin word 'arbor' which means the tree. The term cascade molecules is also used to address them, but 'dendrimer' is the best established one. Dendrimers are a novel class of spheroid/globular nano scaled macromolecules which are characterized by highly branched tree like structures that provides a high degree of surface functionality and versatility. Due to their multivalent and mono disperse character dendrimers have stimulated wide interest in the field of chemistry biology, especially in applications like drug delivery, gene therapy and chemotherapy. Dendrimers are also referred as polymers of 21st century. In fact they possess more favourable properties than the conventional linear polymers. The table.1 lists out the Comparison of the properties of the dendrimers with the linear polymers. Dendrimers exhibit characteristics features of Dendrimer both molecular chemistry and polymer chemistry. Molecular chemistry like properties are due to their step by step controlled synthesis while it shows polymer chemistry like properties as it is made up of monomers [2].

II. STRUCTURE AND CHEMISTRY OF DENDRIMERS

A typical dendrimer is comprised of three different parts, which are

- a focal core
- Building blocks with several interior layers (generations) composed of repeating units, radically attached to the interior core
- Multiple peripheral functional groups (end groups/terminal groups) attached to the outermost interior generations

There continues to be a debate about the exact structure of dendrimers, in particular whether they are fully extended with maximum density at the surface or whether the end-groups fold back into a densely packed interior. Dendrimers can be prepared with a level of control not attainable with most linear polymers, leading to nearly monodisperse, globular macromolecules with a large number of peripheral groups as seen in Figure 1.

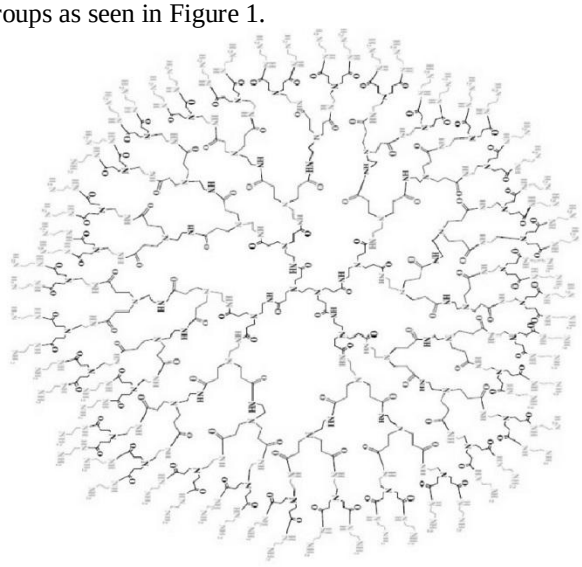

Figure.1 Schematic representation of a generation G4 dendrimer with 64 amino groups at the periphery.

III. TYPES OF DENDRIMERS

Dendrimers are broadly classified on the basis of the core of the molecule, monomer, and its application. They are,

- PAMAM Dendrimers
- PPI Dendrimers
- Chiral Dendrimers
- Multilingual Dendrimers
- Tecto Dendrimers
- Hybrid Dendrimers
- Amphiphilic Dendrimers

- Frechet type Dendrimers
- Peptide Dendrimers
- PAMAMOS Dendrimers

IV. SYNTHESIS OF DENDRIMERS

Dendrimers are synthesized by three methods which are as follows

- Divergent method
- Convergent method
- Double exponential and mixed method

Among the above methods the first two are most used worldwide.

A. Divergent method

In the divergent approach, used in early periods, the synthesis starts from the core of the dendrimer to which the arms are attached by adding building blocks in an exhaustive and step-wise manner.

B. Convergent method

In the convergent approach, synthesis starts from the exterior, beginning with the molecular structure that ultimately becomes the outermost arm of the final dendrimer. In this strategy, the final generation number is pre-determined, necessitating the synthesis of branches of a variety of requisite sizes beforehand for each generation [4].

C. Double Exponential and Mixed Method

It is most advance and recent method of dendrimers synthesis. This is a mixture of both divergent and convergent method. In this method a single starting material is taken from which two monomers are prepared by divergent and convergent method. Then these two monomers are reacted together to give an orthogonal protected trimer. This protected trimer may be use to repeat the growth process again.

V. UNIQUENESS OF DENDRIMERS

A. 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 [5].

B. 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 [5-8].

C. Monodispersity

Dendrimers are monodisperse in nature i.e. they have isomolecular species, whose molecular size, shape and disposition of organic moieties are adjusted and controlled [9].

D. Viscosity

In solution dendrimers form a tightly packed ball which influences its rheological properties. The intrinsic viscosity dendrimers solution does not exhibit linear relationship with mass but it is highest for a specific generation and then it begins to decrease.

E. Electrostatic interactions

Molecular recognition events at dendrimer surfaces are distinguished by the large number of often identical end-groups presented by the dendritic host. When these groups are charged, the surface may have as a polyelectrolyte and is likely to electrostatically attract oppositely charged molecules [10]. One example of electrostatic interactions between polyelectrolyte dendrimers and charged species include the aggregation of methylene blue on the dendrimer surface and the binding of EPR probes such as copper complexes and nitroxide cation radicals [11, 12].

F. Covalent conjugation strategies

The strategy of coupling small molecules to polymeric scaffolds by covalent linkages to improve their pharmacological properties has been under experimental test for over three decades [13-16]. In most cases, however, the conjugated dendritic assembly functions as ‘pro-drug’where, upon internalisation into the target cell, the conjugate must be liberated to activate the drug.

G. Polyvalency

Polyvalency is useful as it provides for versatile functionalization; it is also extremely important to produce multiple interactions with biological receptor sites, for example, in the design of antiviral therapeutic agents.

H. Self-assembling dendrimers

Another fascinating and rapidly developing area of chemistry is that of self-assembly. Self-assembly is the spontaneous, precise association of chemical species by specific, complementary intermolecular forces. Recently, the self-assembly of dendritic structures has been of increasing interest [17]. Because dendrimers contain three distinct structural parts (the core, end-groups, and branched units connecting the core and periphery), there are three strategies for self-assembling dendrimers. The first is to create Dendrons with a core unit that is capable of recognizing itself or a ditopic or polytopic core structure, therefore leading to spontaneous formation of a dendrimer [18-21]. A self-assembling dendrimer using pseudorotaxane formation as the organizing force was reported by Gibson and co-workers [22].

Table.1 comparison between dendrimers and linear polymers

Property	**Dendrimers**	**Linear Polymers**
Structure	Compact, Globular	Not compact
Synthesis	Careful & Stepwise growth	Single step condensation
Structural control	Very high	Low
Architecture	Regular	Irregular
Shape	Spherical	Random coil
Crystallinity	Non-crystalline	Semi crystalline / crystalline
Aqueous solubility	High	Low
Non polar solubility	High	Low
Viscosity	Nonlinear relationship with molecular weight	Linear relation with molecular weight
Reactivity	High	Low
Compressibility	Low	High
Polydispersity	Monodisperse	Polydisperse

The above table shows the comparison of properties of dendrimers with conventional linear polymers. When comparing dendrimers with other nano scale synthetic structures (e.g., traditional polymers, buck balls, or carbon nano tubes), these are either highly non-defined or have limited structural diversity. Dendrimers have some unique properties because of their globular shape and the presence of internal cavities. The most important one is the possibility to encapsulate guest molecules in the macromolecule interior. This makes the dendritic molecules the most useful drug delivery carriers.

VI. ADVANTAGES OF DENDRIMERS

The following properties of the dendrimers makes them as an ideal drug carriers.

- *Enhanced permeability and retention effect:*Size of dendrimers i.e. (Generation 4-4.4 nm) is in nano range. Cancer cells have leaky membranes and having higher biopermeability for anticancer drugs. Lymphatic system is one way and drug loaded dendrimers may get retained inside [23-25]**.**
- *High permeability:* Dendrimers can cross bio-barriers like blood brain barrier, cell membrane. Nanometre range and uniformity in size enhance their ability to cross cell membranes and diminishes the risk of undesired clearance from the body through the liver or spleen [26-28]**.**
- *Sustained /extended effect:* Dendrimers releases drug in a sustained manner. PAMAM dendrimers exhibited slower release, higher accumulation in solid tumors, and lower toxicity. Conjugation with Polyethylene glycol on the surface of these nanocarriers avoids non-specific interaction with plasma proteins or engulfment. Increase in blood circulation time is essential to achieve desired clinical effect [29]**.**
- *Higher Solublization Potential:*Ionic interaction, hydrogen bonding and hydrophobic interactions are probable mechanism by which dendrimers show its solubility enhancing property. Most anticancer drugs have poor solubility and can be loaded into dendrimers to improve solubility [30-35].
- *High uniformity and purity:*The synthetic process used produces dendrimers with uniform sizes range, well defined surface functionality, and negligible impurity. Monodispersed dendrimers would facilitate us to attain targeted drug delivery [36, 37].
- *Multifunctional platform:*Free surface groups can form complex or conjugates with drug excellent molecules or ligands by using cross linking agents. The surface of dendrimers may be conjugated with ligands, solubility modifiers, and stealth molecules [38-40]**.**
- *High loading capacity:* Dendrimers structures can be used to load and store a wide range of organic or inorganic molecules by encapsulation and absorption on surface. Drug can get entrapped inside the internal cavities as well as electro statically in the surface of dendrimers [41, 42].
- *High stability:* Dendrimers drug complex or conjugate demonstrate good stability
- *Low toxicity:* Most dendrimers systems display very low cytotoxicity levels [43-44].
- *Low immunogenicity:*Dendrimers shows low or negligible immunogenic response when injected or used topically [45, 46]**.** The problems in vesicular system like chemical instability, drug leakage, aggregation and fusion during storage, solubility in physiological environment, lysis of phospholipids, purity of natural phospholipids lack in dendritic system.

VII. VII.APPLICATIONS IN DRUG DELIVERY

In 1982, Maciejewski proposed, for the first time, the utilization of these highly branched molecules as molecular containers [47]. Host-guest properties of dendritic polymers are currently under scientific investigation and have gained crucial position in the field of supra molecular chemistry. Host-guest chemistry is based on the reaction of binding of a substrate molecule (guest) to a receptor molecule (host) [48]. Considering the above said properties of the dendrimer, they can be used as novel nano carriers for many utilities. They can be used as

- Solubility enhancers
- Cancer drug delivery
- Targeted and Controlled drug delivery
- Gene delivery
- Cellular drug delivery
- Cosmetics
- Transdermal drug delivery

A. Dendrimers as solubility enhancers

Dendrimers are unimolecular micellar in nature because these have both hydrophobic and hydrophilic layer. Hydrophobic 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 and hydrophobes [9, 49]. The unique properties of dendrimers make them a desirable platform for concurrent delivery of water soluble and insoluble drugs. For instance, the hydrophobic core contains a cavity that can encapsulate hydrophobic drugs. The multivalent surface, on the other hand, can be conjugated with hydrophilic drugs. By taking advantage of the dendrimer structure, Tekade et al. co-encapsulated methotrexate (a hydrophobic chemotherapeutic agent) and all-trans retinoic acid (a hydrophilic compound with mild anticancer activity) in a generation 5 poly (propyleneimine) dendrimer [50]. In this dual drug-loaded dendrimer formulation, methotrexate was loaded into the hydrophobic cavity whereas the small retinoic acids were lodged inside the small voids between branching clefts. Electrostatic interactions between the carboxyl groups of the drug molecules and the amine terminal groups on the dendrimers helped to stabilize the loaded drugs and also gave rise to a pH-dependent drug-release profile. Under acidic condition, deprotonation of the carboxylic group and conformational change of the dendritic structure accelerated the release of drugs from the dendrimer particles. Under neutral and alkaline pH, however, much slower release kinetics were observed. The pH-triggered drug-release property could reduce systemic toxicity by minimizing premature drug leakage during the circulation period. Only upon endocytic uptake by the target cells would the vehicle releases its drug payloads.

B. 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 [49]. Water soluble dendrimers are capable of binding and solubilising small acidic hydrophobic molecules with antifungal or antibacterial properties. The bound substrates may be released upon contact with the target organism. Such complexes may be considered as potential drug delivery systems [51,52]. Once a dendrimer carrying an encapsulated drug reaches the intended site of action, the guest molecule generally must be released to gain bioactivity. Indeed, a concern is that the active drug would ‘‘leak’’ out prematurely, thereby reducing the amount available for the intended therapeutic intervention, or more ominously, result in systemic toxicity. Reassuringly, early experiments showed that the close packing of dendritic branches on the surface of the macromolecule (Fig. 1) effectively formed a ‘‘membrane’’ that reduced diffusion to immeasurably slow rates [53]. In other cases, the release of encapsulated guest molecules was relatively faster, occurring over a few hours, apparently through hydrolytic degradation of the dendrimer in aqueous conditions [54]. The observation that guest molecules could be liberated at different rates demonstrated that viable opportunities exist to tailor the release for either slow or rapid delivery. At present, additional control of delivery rates is being sought; for instance, the ability of a dendrimer to instantaneously release its entire drug payload upon reaching its cellular target would be valuable. Promising steps in this direction are being taken by the development of pH-sensitive materials [54], the fine tuning of hydrolytic release conditions, and the selective liberation of guest molecules on the basis of their size or shape [55].

C. Dendrimers in Gene Delivery

Dendrimers can also carry siRNA through surface electrostatic interactions. A generation- 3 nanoglobular dendrimer (poly-l-lysine) octa (3-aminopropyl) silsesquioxane) surface modified with a tumor-targeting peptide, c (RGDFK), has been reported to carry both doxorubicin and siRNA for targeted combination therapy [56]. These siRNA–dendrimer complexes were readily internalized by U-87 glioblastoma cells via receptor-mediated endocytosis and showed significant gene-silencing activity. The delivery of small molecules complexed as guest molecules in internal void spaces of dendrimers is, at least in retrospect, intuitively obvious. By contrast, the delivery of extremely large macromolecules, such as MDa-sized plasmid DNA for non-viral gene therapy, is counter-intuitive because the encapsulation of a ‘‘guest’’ molecule many times the molecular weight of the dendrimer itself appears impossible. Nonetheless, experimental evidence had demonstrated that gene delivery strategies also benefit from the participation of dendrimers l58]. For example, from its original discovery of efficacy for gene delivery [59], the fractured form of PAMAM, known as Superfect TM, is now a commercially-available transfection agent for in vitro applications [60]. Typical approaches to optimize dendritic gene delivery for in vivo use have involved the surface modification of a PAMAM backbone, either with arginine [61] or hydroxyl groups [62]. Alternatively, the results reported by Kim and co-workers, who demonstrated improved gene delivery with a novel PAMAM-PEG-PAMAM triblock copolymer, show that construction of dendrimers composed of new building blocks is warranted [61]. Although still in their infancy, there are efforts afoot to exploit dendrimers for the delivery of smaller nucleic acids such as antisense oligonucleotides and short interfering RNAs (siRNA); the success of these applications is likely to depend on the continuing development of novel materials for dendrimer synthesis [62].

D. Dendrimers as cellular drug delivery carrier

Tests showed that the pure drug (Ibuprofen) takes 3 hours to enter the cell membrane whereas the dendrimer-drug complex have taken only 1hour to enter the cell membrane. This conforms that the dendrimers can carry the complex drug efficiently inside the cell [49].

E. Dendrimers in cosmetics

Dendrimers have a great contribution in cosmetics. Various cosmetics industry uses dendrimers in formulation. L'Oréal has a patent for using dendrimers in the production of cosmetics like mascara and nail polish. Unilever also have a patent for dendrimers in the production for used in spray, gels and lotions [63, 64, 65].

F. Transdermal drug delivery:

Clinical use of NSAIDs is limited due to adverse reactions such as GI side effects and renal side effects when given orally. Transdermal drug delivery overcomes these bad effects and also maintains therapeutic blood level for longer period of time. Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. Dendrimers have found applications in transdermal drug delivery systems. Generally, in bioactive drugs having hydrophobic moieties in their structure and low water solubility, dendrimers are a good choice in the field of efficient delivery system [66].

VIII. CONCLUSION

Ever since the discovery of dendrimers there has been a rapid increase in the importance in chemistry. For the past two decades the dendrimers have been researched for a lot properties and every possible applications. Even though there are many difficulties in the multi-step synthesis, these dendrimers has been the favourite for many applications. Their unique properties makes them a smart choice for a drug delivery application. Despite their multiple advantages in the delivery of the drugs, the difficulties in the synthesis and their in-vivo behaviour has kept the dendrimer technology in its infancy even after almost three decades. Dendrimers should be more commercialized and freely available so as to use them in more advanced studies in the future. By that way when we realize the full potential of the dendrimers there will be possibilities of brighter future.

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