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A REVIEW ON DENDRIMERS: THE NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Dendrimers are a new way to send drugs that could be useful because they get around many of the problems with older methods. Dendrimers have been around for a while. This page talks about their past, what makes them unique, how they are made, and how they are used to deliver drugs. Some of the benefits of dendrimers are better drug solubility, controlled release, and less toxicity. They are defined by their high symmetry, surface polyvalency, and monodispersity. Medicines, genes, and imaging chemicals are just some of the restorative materials that can be contained by them. The physiological properties of dendrimer-drug conjugates are better and they work better than free medicines. A lot of different methods, like convergent and divergent growth approaches, are used in dendrimer synthesis to finetune their structure and features. Biodegradable dendrimers could also be used to deliver medications precisely and over a long period of time. Because they are flexible and easy to control, dendrimer structures can be used in many biological ways. These include treating cancer, delivering vaccines, and transfecting genes. Even though they show promise, problems with toxicity and building up synthesis processes still exist. Dendrimers haven't been used a lot in therapeutic settings yet, but that's starting to change as study and technology keep getting better.

KEYWORDS: Dendrimers, Drug delivery, Nanomedicine, Synthesis, Biocompatibility, controlled release, Conjugates, Biomedical applications.

INTRODUCTION

It has been reported that a number of pharmacologically active drugs have issues with water solubility, half-life, specificity, and biocompatibility. Products that are created in crystalline solid forms, amorphous forms, formulations based on lipids, and polymer drug conjugates are some of the ways that are utilised in order to address these differences and improve the release qualities of these treatments. With that being said, there are worries over the toxicity and stability of these technologies.[1] Therefore, nanoparticles-assisted medication delivery has recently been the subject of extensive research in order to achieve the goal of concurrently distributing and targeting diagnostic agents and treatments within a single system. This is accomplished by utilising biodegradable and biocompatible polymers throughout the process.[2] Polymers are distinguished by a number of characteristics, including enhanced drug solubility, drug targeting capabilities, and biocompatibility, to name a few. Therefore, there have been a great number of applications of the advancements that have been made in polymer research, including their use in the enhancement of drug delivery.[3] Polymers can be classified into one of four categories: linear, cross-linked (including side chains or functional groups), branching, or perfect. The majority of polymers fit into one of those categories. The chemical structures of classic linear polymers, such as polyethylene glycol (PEG), polyglutamic acid, polysaccharide, poly (allylamine hydrochloride), and N-(2-hydroxypropyl) methyl acrylamide, are frequently ambiguous and unclear. This is despite the fact that these polymers have gained general approval for use in clinical settings.[4]

Dendrimer: A brief History and Its unique properties

A tree, meros, or branch is what the Greek word "dendron" means, and the English word "dendrimer" is an archaic noun that is derived from this word. In 1978, Buhleir and his colleagues synthesised and reported dendritic polymers, which were initially classified as "cascade" and "nonskid-chain-like" molecules with molecular cavity topologies. These molecules were the first to be identified as dendritic polymer.[5] Between the years 1979 and 1985, Donald A. Tomalia and his colleagues at Dow Laboratories made significant technological advancements in the field of dendrimers.[6] Tomalia was responsible for the formation of dendrimers, which are polymers that have a hollow centre and tendrils that branch out into one other in a manner that is known to be regular and predictable. The work of these two study groups helped shape the early history of dendrimers in some ways. Some of the best known types of dendrimers are polyamide-, polyether-, polyester-, and

phosphorus-based [dendrimers; polypropyleneimine (PPI) dendrimers; and polyamidoamine (PAMAM) dendrimers. Up to now, more than one hundred dendritic patterns have been found.[7] Also, as different manufacturing methods have been improved, many new dendrimers have been created that can be made quickly and have a wide range of structures. Because of the progress that has been made, there has been a huge increase in the use of dendrimers in chemistry, materials science, biology, and medicin.[8] Because they are monodisperse, have high symmetry, and have surface polyvalency, dendrimers are different from other linear polymers. In dendrimer synthesis, a number of growth reactions are used over and over again to increase the amount of branching and generation. This results in the formation of a three-dimensional spherical structure. Dendrimers have a core-shell form that is well defined and a polydispersity that is limited.[9] The reason for this is the specific chemical process they go through. This can be seen in higher generation dendrimers, which tend to be bigger, have a bigger internal cavity, and have more functional groups connected to the ends of them. The goal of these methods is to find out what the monodispersity features and effective charge of dendrimers are.[10]

The purity of surface-charged PAMAM dendrimer nanoparticles, as well as their electrophoretic mobility and molecular charge distribution, can be evaluated by the use of capillary electrophoresis.[11] According to the findings that Jackson and his colleagues released in 1998, transmission electron microscopy (TEM) was able to validate the nanoscopic characteristics of individual PAMAM dendrimers from generations 5 to 10 (G5 to G10). When using PAMAM G5, the average diameter is 4.3 nm, however when using PAMAM G10, it increases to 14.7 nm.[12] In addition to their nanoscopic nature, dendrimers are extremely adaptable and may be easily changed or conjugated with a wide variety of chemical species. These chemical species include fluorophores, targeting ligands, medications, and genes.

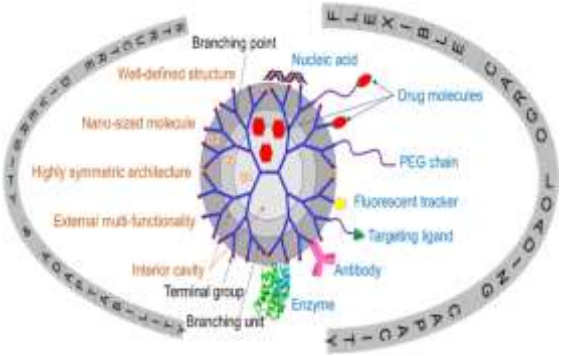

Fig. 1: Properties of dendrimers.

Specific properties of dendrimers

Below, we will go over some key characteristics of dendrimers:

1. The immunogenicity of dendrimers is minimal when they are composed of tiny molecules, include PEG, or have a PEGylated surface.
2. The viscosity of dendrimers continues to decrease as their molecular mass increases.
3. As photo-friendly hosts, dendrimers have potential applications. Dendrimers' peripheral groups can be photochemically modified to control the encapsulation and liberation of guest molecules.[13]
4. Dendrimers have the ability to function as antennae that absorb light very efficiently.
5. Intrinsic viscosity is higher in amine-terminated dendrimers with a complete generation (G1.0, G2.0, and G3.0) than in dendrimers with half generation (G1.5, G2.5, G3.5, and G4.5) that are ester terminated.[14]Intermolecular hydrogen bonding could be the cause of this.
6. Dendrimers can assist decrease medication toxicity and extend residence time in the system by including a wide spectrum of compounds, including pharmaceuticals, metals, imaging chemicals, and more. This makes it easier for the medicine to be released gradually.[15] Also, it may help with inflammation, the HIV virus, and arthritis, according to some reports.

Synthesis of dendrimers

Tomalia et al. originally reported the synthesis of dendrimers in 1985. Dendrimer preparation can be accomplished in various ways; here are just a few:

1. The technique of divergent growth
2. The technique of convergent growth
3. "Hypercores
4. Branched monomers" growth,
5. "Lego" chemistry,
6. "Click" chemistry.

The two most common approaches among them are the divergent and convergent growth strategies.[16]

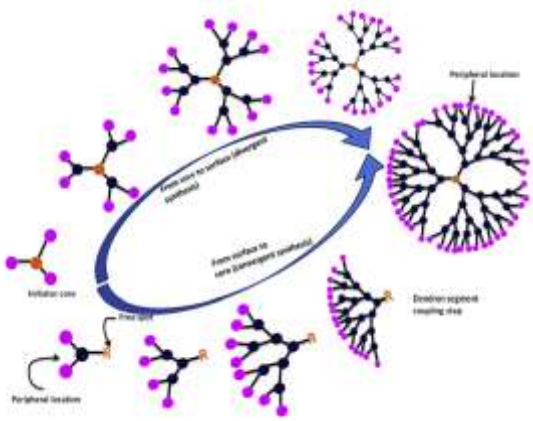

Fig. 2: Synthesis of dendrimers.

Dendrimer-drug conjugates

Dendrimer-drug conjugates have the potential to enhance localised efficacy while decreasing systemic side effects as compared to free medicines. Conjugation with dendrimers is said to lengthen the half-life of medicines. Conjugation with PAMAM dendrimer, for example, extends methotrexate's half-life from 24 minutes to 24 hours. Because of the longer time a drug stays in the bloodstream, it is more effective and patients are more likely to take their medication as prescribed, which increases compliance.[17] Dendrimers are a great way to increase the solubility of medications. For instance, when paclitaxel is coupled with PAMAM dendrimer, its water solubility is increased by a factor of nine thousand. In a prior publication, we detailed our investigation into the therapeutic effectiveness of a DenTimol dendrimer-drug combination in the treatment of glaucoma.[18] This was accomplished by use of a PEG spacer. Over the course of four hours, roughly eight percent of the dendrimer-drug was absorbed through the cornea. This is possible because dendrimer has a great mucoadhesive ability that lets DenTimol cross the cornea easily. In adult male Brown Norway rats that did not have high blood pressure, DenTimol was better at lowering intraocular pressure (IOP) than timolol maleate.[19] It was possible to lower intraocular pressure (IOP) by 7.3 mmHg in less than 30 minutes with a single dose of DenTimol (10 µL of 0.5% w/v timolol). This decrease was a lot bigger than the decrease that timolol PBS eye drops caused by a large amount.

According to the Food and Drug Administration (FDA), dendrimer-drug conjugates could be either new drugs or devices that work with other drugs. It is possible that this issue with bureaucratic regulation may be avoided if pharmaceuticals could be separated from dendrimer-drug conjugates while still preserving their original structure.[20] Because of this, it is extremely important to investigate how dendrimer-drug conjugates release their respective

medicines. The most straightforward approach includes establishing a link between the medicine and the dendrimer that is either cleavable or stimuli-liable. When it comes to cancer cells, glutathione and reactive oxygen species (ROS) have the ability to cleave disulfide linkers, whereas thioketal linkers are more difficult to break.[21] Cleavable dendrimer-drug conjugates have made widespread use of them as a result of this rationale. Because the microenvironments of tumours are acidic, dendrimer-drug conjugates for cancer therapy also incorporate pH-responsive linkers.[22] These linkers include acid-liable bonds, such as the acetal bond. We have created a medication delivery system that is based on dendrimer-camptothecin and is constructed out of hydrogel. A significant increase in tumour inhibition was achieved with the use of the regulated self-cleaving release approach, which extended the release of CPT.[23]

Dendrimers as drug delivery vehicles

When it comes to developing nanomedicine to treat different diseases, dendrimers have become an essential class of nanostructured carriers. Dendrimers' structural variety and adaptability have led to their numerous applications in gene and medication delivery. An example of this would be dendrimers that have a hydrophobic core and a hydrophilic outside, which have the potential to function as unimolecular micelles.[24] This technique has been utilised to solubilize medications that are hydrophobic by entrapping them within the intramolecular cavity. Cationic dendrimers are an example of a common non-viral gene carrier that has seen considerable application.[25] It is feasible to conjugate dendrimer surface groups with functional moieties, including pharmaceuticals and other functional moieties be an effective method for enhancing the stability and solubility of pharmaceuticals. The formation of a unimolecular micelle is the result of a process known as PEGylation of dendrimers, which involves the conjugation of PEG chains to dendrimers.[26] When nanomaterials are endowed with dendrimer-polysaccharide conjugates, they frequently exhibit good binding properties and increased compatibility. Chitosan, hyaluronic acid, cyclodextrin, and dextran are only few of the polysaccharides that have been related to dendrimers after extensive research. A PAMAM dendrimer that was combined with hyaluronic acid displayed increased tumour penetrating property.[27]

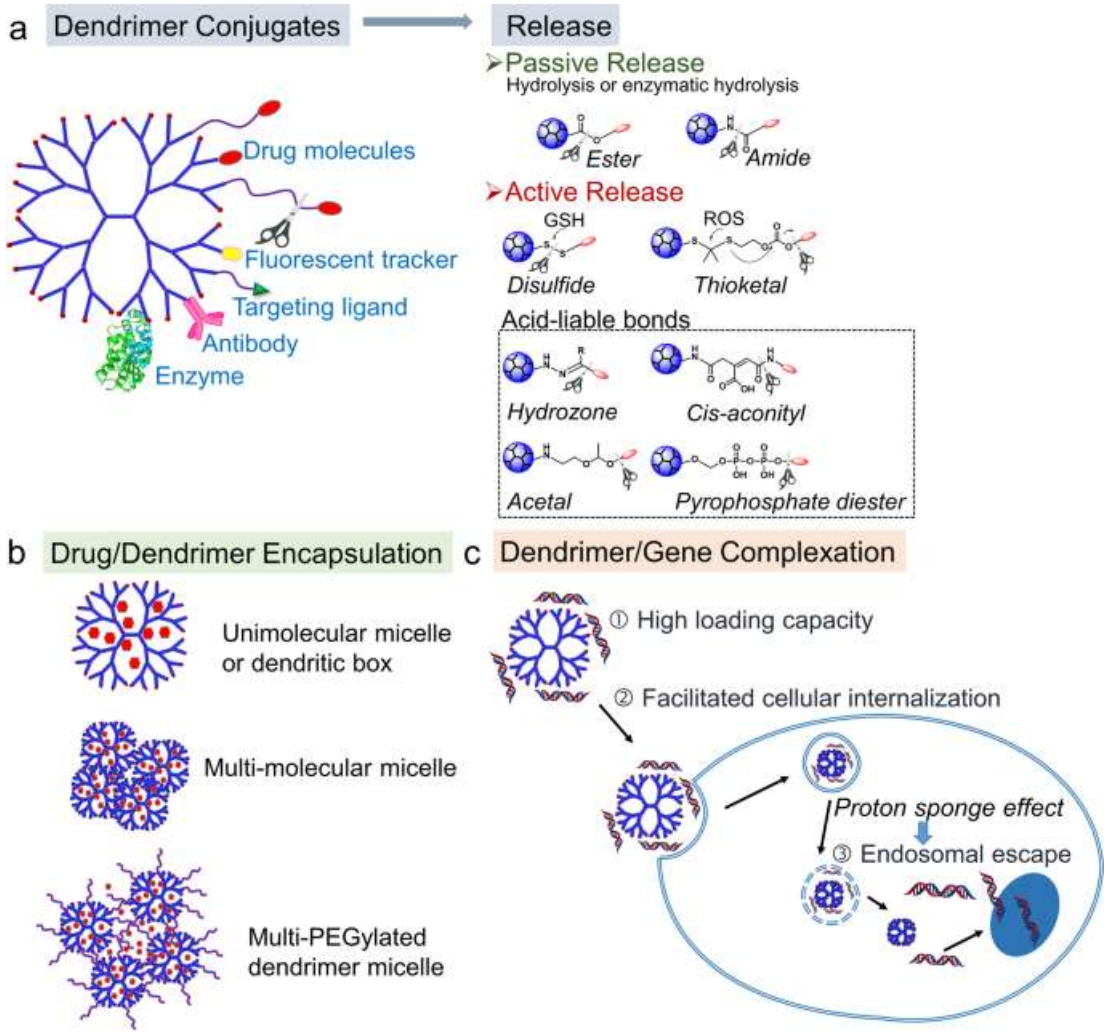

Fig. 3: Dendrimers as drug delivery vehicles.

Drug-loaded dendrimer as nanovehicles

Dendrimers resemble trees and have cores that are similar to their trunks, with branches that branch out to other units that resemble interior shells. In the case of dendrimers, these units can be connected to surface functional moieties through their leaves.[28] The centre is protected from the outside world by increasing the density of branches surrounding it. The dendrimer's interior branches and shells encapsulate the drug molecules through noncovalent interactions, such as hydrophobic, physical entrapment, or ionic forces, which retain the guest molecule inside the dendrimer through a "click in" mechanism.[29] And because a pH below seven causes the protonation of amide groups, which in turn causes them to separate from the host molecule and ultimately deliver the medicine to the tumour site, the resulting weak interaction feature can be useful in this process.[30]

However, the complex's 1 H nuclear Overhauser effect spectroscopy (NOESY) spectra showed an abundance of intermolecular NOESY cross-peaks, suggesting that the dye was

quite close to the dendrimers, which in turn limited the mobility of the encapsulated dye.[31] G4.0 PGLSA dendrimers have the ability to encapsulate hydrophobic anticancer medicines, making them a viable drug-delivery technology.[32] This capability could be employed in the development of numerous such medications. For example, even when enclosed in G4.0 PGLSA dendrimers, 10-hydroxy camptothecin significantly decreased tumour cell viability in cytotoxicity tests using human breast cancer cells.

Simple dendrimers in gene transfection

By introducing functional genes into the affected cells, gene therapy attempts to fix genetic abnormalities. Due to their susceptibility to degradation by enzymes, nucleic acids (NA) cannot be transported directly via the bloodstream for this purpose. In order to transfer genes, a carrier is needed.[33] Viruses were once the go-to choose, but their use was limited because of all the problems they caused (such as the immunogenic proteinaceous capsid). Thus, an ideal DNA vector would exhibit the following properties: target specificity, high transfection efficiency, biodegradability, stability, minimal toxicity or immunogenicity potential, ease of design and production, and so on.[34] Because this combination both facilitates endosomal egress and protects NA from enzymatic degradation, dendrimers were chosen as the gene transfection agent of choice.[35] Dendriplexes were created by drawing inspiration from lipoplexes and polyplexes, which are complexes of NA with liposomes and linear polymers, respectively. Dendrimers that have positively charged groups on them are called dendriplexes, and they can bind with NA. Because of their abundance of ionizable end groups, they can bind a great deal of genetic material.

Pegylated dendrimers in cancer therapy

This process, which is referred to as PEGylation, involves the conjugation of PEG to the dendritic scaffold. When it comes to drug loading, targeting, and solubilization, PEGylated dendrimers work better than other options. This is because the PEG chains that are connected to them are more effective. Aside from that, they are less immunogenic, antigenic, and poisonous when taken up by macrophages.[36] In addition, they don't cause hemolysis and have a short half-life compared to other drugs. They are a good choice for anticancer drugs that directly target tumours because they have many benefits. You can make dendrimers last longer without losing their usefulness by PEGylating them.[37] This makes them more stable because the surface crowds them together, which also makes them move more slowly.[38] A mix of drug-conjugated PEGylated dendrimers can be made by first adding hydrophobic

drugs to the dendrimers and then adding polyethylene oxide (PEO) groups to the outsides of the dendrimers.

Drug delivery

Dendrimers are a good way to deliver drugs because their structure can be controlled and their terminal functional groups are more reactive than those in other polymers. The PAMAM dendrimers are being studied by researchers as a possible way to deliver medicines by mouth.[39] They have a branching structure that dissolves in water. But when they're in a solution, they become small and round.[40] New studies say that these dendrimers are very good at opening up tight junctions and can move through both paracellular and transcellular routes. Creating drug delivery systems for NSAIDs is what dendrimer science is mostly about. Because they have amino groups on the ends, dendrimers of the PAMAM or PPI types can dissolve these medicines that are hard to mix with water.[41]

Therefore, the medicine can be encapsulated by their structure. When designing new drug delivery systems for precise targeting, biodegradable dendrimers are the way to go. Dendrimers have the medications attached to them in various methods, including chemical conjugation and physical encapsulation.[42] They are more important and used in medicine delivery since they are biodegradable.

CONCLUSION

One promising new platform for the delivery of different moieties is dendrimers. Notable features of dendrimer-based carriers are their molecular weight, size consistency, low PDI, and adaptability. Among the many potentials 21st-century applications for dendrimers in fields as diverse as photodynamic treatment, medicine, gene delivery, pharmaceuticals, biopharmaceuticals, imaging, oligonucleotide delivery, vaccine administration, and siRNA delivery, dendrimers stand out. One way to broaden dendrimer's use is to give it biodegradable characteristics. Two methods, the divergent growth method and the convergent growth method, are available for their synthesis. These compounds include a central molecule, branches, and peripheral groups. More recently, dendrimer creation has also made use of a handful of approaches, such as click chemistry, lego chemistry, and the double exponential growth method. In addition, dendrimers are perfect carriers due to their adaptability in structure. Dendrimers are ideal carriers for a wide variety of applications due to their easily controllable topographies, which include size, shape, liposome locking, branching length, PEGylation, surface functionality, and the ability to synthesise targeted

dendritic scaffolds according to specific needs. Dendrimers can be categorised as PAMAM, PPI, glyco, LC, peptide, etc., according on the sorts of core and peripheral groups they include. Affordable synthesis, industrial-scale synthesis, and the resolution of specific toxicity concerns all necessitate more investigation. Dendrimers have evolved into a promising choice for drug delivery and clinical.

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