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DENDRIMER CHEMISTRY AND HOST-GUEST INTERACTIONS FOR DRUG TARGETING

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ABSTRACT: The objective of this review was to bring a chemicophysical approach towards dendrimers in different aspects including host-guest interaction and drug targeting. These nanosized polymeric molecules are unique in structural properties which have made dendrimers a potential candidate to lend itself as a carrier for drugs and bioactive molecules. Dendrimers offer the coupling of guest molecules by several phenomena including internal complexation and topological complexation forming catenanes and rotaxanes. Surface binding of guest molecules are achieved by coupling with the multiple surface binding groups. The physical attributes like size, shape, molecular weight and surface charge are modified for internalization of dendrimers into the specific cells by passive targeting mode. The polymer-drug couples are linked to targeting ligands for their active targeting by receptor mediated endocytosis. The binding and dissociation kinetics of such molecules can be tuned according to the desired retention time in a biological system.

INTRODUCTION: Dendrimers belong to the family of nanosized, three dimensional polymers having a unique architecture resembling tree like branching and a compact sphere like geometry in solution phase. The name dendrimer is derived from the greek word "Dendron", which means "tree". The journey of research in dendrimers begins from 1970 and was started by Vogtle and co-workers. They first studied the controlled synthesis of dendritic arms. They produced polymeric branching units with large molecular cavities by repetitive reactions of mono- and diamines with a central core molecule [1].

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The first hyperbranched family of dendrimers was developed by Tomalia and his team in 1984, where they induced coupling of ethylene diamine to a central ammonia core to produce the "starburst dendrimers" [2].

Dendrimers possess individual branching called dendrons radiating from the central core, where the concentric branching layers form a complete generation, denoted by 'G' and is designated with a specific generation number. Due to the unique branching behaviour, dendrimers possess well defined molecular weight, size and number which can be increased with a controlled manner with requirement of the investigator [3, 4].

The dendrimers have potential to create new opportunities in chemistry, biology and medicines fields, for this reason, over the past three decades, different synthesis strategies were developed to create new dendrimers families.

This review is specifically based on different dendrimer families, their synthesis, host-guest interaction, self-assembly and self-organization along with active and passive targeting of dendrimers.

Property based classification of Dendrimers: Dendrimers vary from each other in their physical and chemical properties, though they have a similar geometric architecture. The chemical properties of the branching element (dendrons) and surface groups solely decide their physical nature. The different families of dendrimers are discussed below.

1. **Hydrophilic dendrimers:** These are the first synthesized and commercialized poly (amidoamines) dendrimers. The synthesis of PAMAM dendrimers involves the reaction between an alkyl diamine core [e.g. ethylene diamine (EDA)] with methyl acrylate monomers to produce branched intermediate, which can be transformed to the smallest generation of PAMAM dendrimers with OH or NH_2 surface groups, upon reaction with ethanolamine and excess EDA respectively. Hydrolysis of the methyl ester in this intermediate produces the smallest anionic dendrimers (G 0.5) with four COOH groups [2, 3, 5].

   The starting reaction involves Michael addition and for synthesis of higher PAMAM dendrimers sequential Michael addition of methyl acrylate monomer followed by amidation reaction with ethylene diamine is performed. The dendrimer growth reaches a critical point, which generally starts from G7 and decrease in synthetic yield is observed until reaching G10 [6, 7]. This phenomenon is due to the steric factor which is the result of overcrowding of branching arms. This phenomenon is termed as the 'de Gennes dense packing effect' [5]. The PAMAM dendrimers are considered ideal carriers for delivery of drug molecules due to their high aqueous solubility, large variety of surface groups and unique architecture [8, 9].

2. **Biodegradable dendrimers:** The emergence of biodegradable dendrimers was to produce the desired large molecular weight carriers that can achieve a high accumulation in tissue and allow fast elimination of its fragments through urine to avoid non-specific toxicity. These are generally prepared by inclusion of ester groups in the polymer backbone, which will be chemically and/ or enzymatically cleaved in physiological solutions.

   The factors controlling the degradation of such dendrimers includes: the nature of chemical bonds, the hydrophobicity of monomer units, size of dendrimers and cleavage susceptibility of peripheral and internal dendrimer structure [10, 11]. Because of their biodegradability and biocompatibility, polyester dendrimers are utilized for delivery of anticancer drugs and gene delivery. However, the non-specific hydrolysis mechanism and long term degradation have switched on the further research for obtaining specific spatial and temporal degradation behaviour [12].

3. **Amino acid based Dendrimers:** This family of dendrimers were developed to integrate the properties of the amino acid building blocks including chirality, hydrophobicity/ hydrophilicity, biorecognition and optical property. Chirality of amino acid based dendrimers is a combined effect of product of the chirality of the core, branching units and terminal surface groups. Optically active amino-acid based protein mimetic dendrimers have been synthesized using amino acid library [13, 14].

   The specific internal composition originated by amino acid building blocks offers stereoselective sites, where guest molecules can be attached non-covalently. These dendrimers can be used as protein mimetic, gene delivery carriers and for targeted drug delivery, due to their unique structural folding of the branching units. This family of dendrimers are generally synthesized either by amino acids or peptide grafting and displayed on the conventional dendrimer surface or attachment of amino acids or peptides to a peptide or organic core [15].

4. **Glycodendrimers:** The origin of glycodendrimers is based on the fact that the carbohydrate interacts with different receptors displayed on cell surface, which in turns

controls several normal and abnormal processes. This interaction was found to be strong for a multivalent ligand- receptor system. So, different researchers have developed macromolecules displaying a large number of carbohydrate ligands using dendrimers as carrier [16].

'Sugar balls' (**Figure 1**) have been prepared, where the surface groups of G2 – G4 PAMAM dendrimers were functionalized with lactose and mannose sugar and the binding specificity was confirmed by the ability of PAMAM-Maltose conjugate to precipitate Concanavalin A, which is a lectin that selectively recognizes and binds the maltose sugar. Glycodendrimers were reported to be utilized as carrier for cancer therapy, as metastatic agent as well as immunostimulant [17, 18].

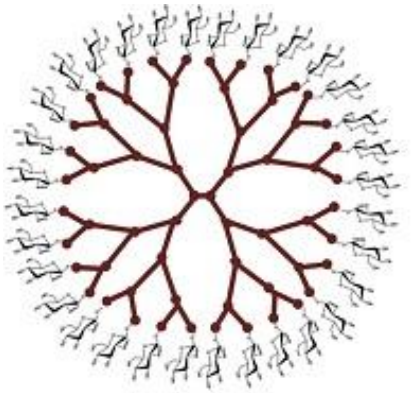

FIGURE 1: SCHEMATIC VIEW OF A GLYCO-DENDIMER (SUGAR BALL), CONSISTING OF PAMAM CARRIER DISPLAYING N- CARBOXY-ANHYDRIDE GLUCOSE SURFACE GROUP [18]

5. **Hydrophobic dendrimers:** The systemic delivery of dendrimers requires sufficient aqueous solubility. But the hydrophobic void regions in the dendritic structure facilitate the better encapsulation and solubilisation of hydrophobic drug moieties. This structure mimics the amphiphilic polymer micelle, but not having a critical micellar concentration (CMC). The building units of dendrimers are covalently attached to each other and resist break down in dilute solution phase. Dendrimers having hydrophobic internal voids and hydrophilic surface resembling unimolecular micelle have been reported and solubility of hydrophobic probes, dyes and fluorescent markers have been studied successfully [19].

Cyclophanes or dendrophanes are dendrimers, reported to encapsulate aliphatic and aromatic moieties. These kind of dendritic structures were also reported to control the release of drugs [20].

6. **Asymmetric dendrimers:** The controlled iterative synthetic steps produce the symmetrical dendritic structure. But a class of novel structures can be synthesized by imparting asymmetry to the dendritic structure, which may offer a better pharmacokinetic profile. These are generally synthesized by coupling dendrons of different generations to a linear core molecule. The final structure forms a non- uniform orthogonal dendritic architecture. The molecular weight, structure and number of functional groups can be tuned in this type of dendrimers.

Frechet and co-workers synthesized the most recognized asymmetrical dendrimers known as 'bow - tie' polyester dendrimers [21, 22] (**Figure 2**). Lee and co-workers utilized 'click' chemistry for synthesizing a G3 asymmetric dendrimer.

The beauty of this dendrimer is that one Dendron can be functionalized for targeting purpose and other orthogonal Dendron for attachment of the therapeutic moiety, which results in net biocompatibility and cell-specificity [23].

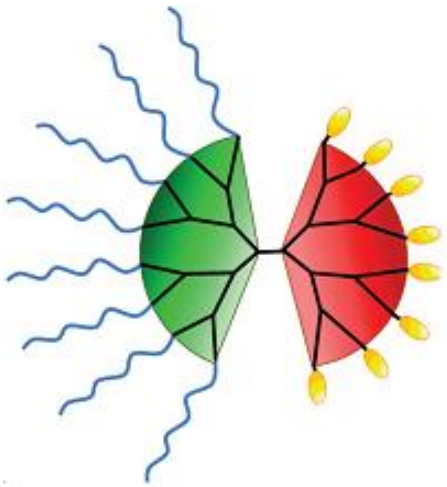

FIGURE 2: ASYMMETRIC DENDRIMER (BOW-TIE TYPE) SHOWING THE LEFT HALF (GREEN PART) FUNCTIONALIZED WITH PEG VIA CARBAMATE LINKAGE, THE RIGHT HALF (RED PART) REPRESENTS THE ORTHOGONAL DENDRON LOADED WITH ANTICANCER DRUG [21]

Synthetic approaches on Dendrimers:

1. **Divergent synthesis:** Divergent dendrimer synthesis is a technique that induces the dendrimer growth from the core towards the periphery in a stepwise fashion by addition of monomer units. The monomer units are coupled to a multifunctional initiator core, where further addition of building blocks to the surface of parent dendrimer to produce successive dendrimer generation. Problems may arise from side reactions and incomplete reactions of the end groups which lead to structural deformations [5].

   For example, incomplete Michael addition reaction produces a fraction of free amine groups and lead to intramolecular cyclization reaction and fusion of the growing branches. High reaction temperature (i.e. more than 80°C) may lead to dendrimer fragmentation via retro-Michael addition reaction. Hydrolysis of the methyl ester groups may occur in aqueous solution which yields carboxylic acid groups [24, 25].

   The unwanted side reactions can be prevented by taking large molar excess of reagents and removal of undesirable by products after each step. Divergent synthesis has its own limitations like difficulty in purifying the final product from structurally similar by products, lengthy multistep reaction and non-ideal growth events [26]. The PAMAM dendrimer family was the first family to be synthesized, characterized and commercialized using divergent synthesis scheme.

2. **Convergent synthesis:** This technique of synthesis was developed to meet the deficiencies of the divergent method. It begins with the dendrimer surface units coupled to additional building blocks to form the branches.

   Hence, the dendrons are synthesized from the periphery towards the focal point. Finally, each Dendron is coupled through its focal point to a multifunctional core to produce the complete dendritic structure. The structural difference between the by-products and the dendrons leads to easy purification [5].

   Although, the number of synthetic steps is same, the occurrence of non-ideal dendrimer growing events is reduced to a great extent, which implies the improved monodispersity of the final dendrimers. The convergent method is also having some difficulties particularly, while synthesizing the higher generations. It has been reported that the yield is reduced for higher generations, which can be due to the steric crowding, lowering the reactivity of dendrons focal point.

   Besides that, the major problem arises at the chromatographic characterization, since the monomer addition does not produce a significant increase in the molecular weight of the product as compare to the parent Dendron [27]. However, a prefabricated lower generation multifunctional hypercore produced from flexible unit to reduce the steric hindrance can be used to increase the yield, which can allows folding of dendritic arms towards core forming dendrimers of oblong geometry and diverse internal void spaces.

3. **Combined synthesis or Double Exponential Growth Method:** Kawaguchi *et al.*, reported a hybrid convergent-divergent dendrimer synthesis method [28]. This method was developed to accelerate the dendrimer synthesis. This method involves the protection of branched monomers with protecting groups, which remain stable during cleavage of the opposing functionality. The selective deprotection of branched monomer surface groups activates convergent monomer or deprotection of focal point activates divergent monomer.

   Coupling of these products gave the first generation dendrimers by divergent approach. The parent dendrons are then exponentially grown by coupling to an activated Dendron. Each additional activation and coupling sequence doubles the final Dendron generation. Final dendritic structure is achieved by coupling the activated dendrons to a central core (**Figure 3**). The combined method not only achieves the rapidity of both kind of synthesis, but also faces the combined disadvantages of both synthetic methods.

The synthesis of higher generation is hindered by steric factor. Protection and activation of monomers needs an efficient reaction scheme [29].

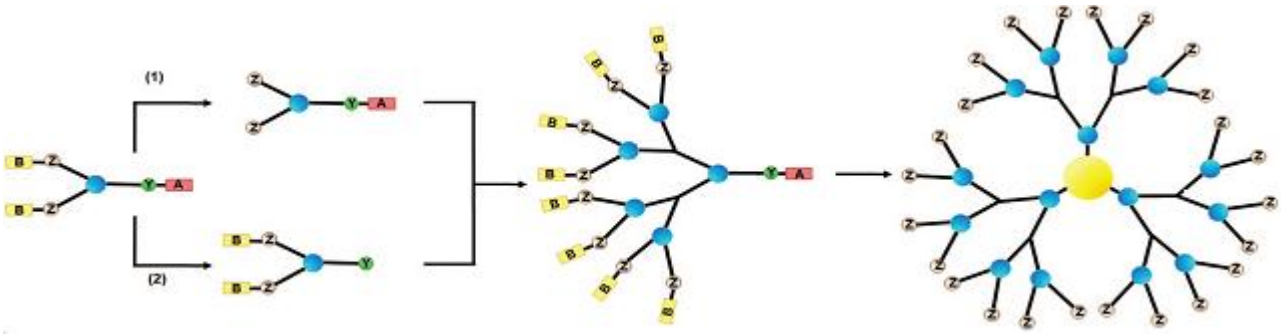

FIGURE 3: SCHEMATIC REPRESENTATION OF A COMBINED CONVERGENT - DIVERGENT SYNTHESIS TECHNIQUE, WHERE THE FOCAL POINT (Y) OF BRANCHED MONOMER AND TERMINAL GROUP (Z) ARE PROTECTED WITH PROTECTING GROUP A AND B RESPECTIVELY. SUITABLE DEPROTECTION TECHNIQUE THEN PRODUCES DUALLY PROTECTED DENDRON AND FINALLY A COMPLETE DENDRITIC STRUCTURE

4. **Click synthesis:** Synthesis via "Click" chemistry is advantageous because of its coupling specificity, mild reaction conditions and quantitative synthetic yields. Salts like NaCl are formed as by-product which can be easily removed. Dendrons produced by this method can be used to produce both symmetric and asymmetric PAMAM dendrimers, with an increase in chemical and architectural versatility [30, 31].

Chemistry of different modes of Host-guest interactions: The unique structural arrangement and availability of multivalent surface groups offer the versatility of dendrimer for guest molecule interaction. The interaction mainly involves supramolecular interactions, including hydrogen bonding, hydrophobic attractions and topological complexation. Encapsulation of drugs uses the bulk of the exterior of dendrimers or interaction between the dendrimer and drug to trap the drug inside the dendrimer having egg shell like structure. Initial studies on dendrimers were based on their use as unimolecular micelle and dendritic boxes. A newer approach for controlling the release of drugs from the encapsulating micellar compartment involves the use of hybrid dendrimers with pH sensitive hydrophobic acetyl groups on the dendrimer periphery [32].

Surface and Internal complexation: The unique structure of dendrimers is proved to create new opportunities for host-guest interaction. Molecular recognition can be achieved by complexing surface agents to the multiple end groups and the small substrate molecules are encapsulated within the internal voids of the dendrimers (**Figure 4**). Dendrimers have also been reported to possess unimolecular micelle properties [33, 34].

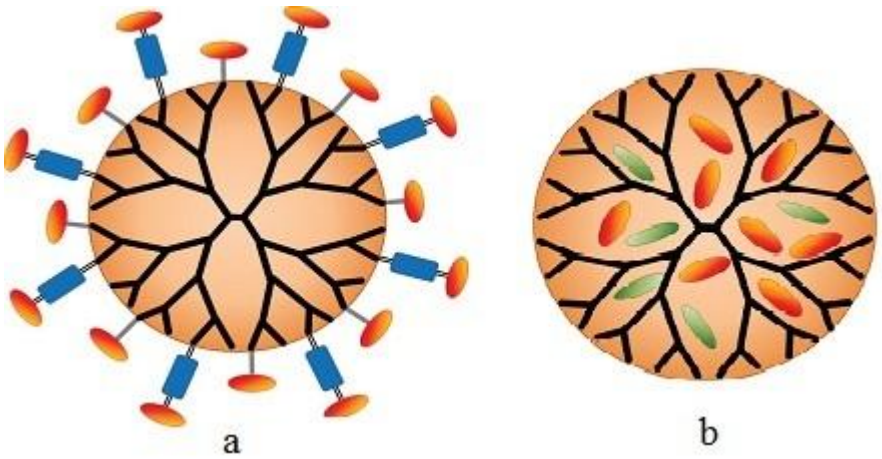

FIGURE 4: SCHEMATIC DIAGRAMS OF DENDRIMERS SHOWING THE CONJUGATION OF DRUG DIRECTLY (RED OVAL) OR BY PH SENSITIVE LINKAGE TO THE SURFACE GROUP (A), HYDROPHOBIC DRUG MOIETIES ENCAPSULATED WITHIN THE VOIDS (B)

Non-specific internal binding: The non-specific internal binding is attributed to the formation of hydrophilic outer layer and hydrophobic interior by coating of dendrimer. The dendrimers gain aqueous solubility and interaction of different molecules internally due to the pH effect on binding. The dendrimers are getting considerable interest as unimolecular micellar carrier for water insoluble drugs or for targeted drug delivery by utilizing the surface groups for cellular specificity [35, 36, 37].

Directed internal binding: It has been reported that dendrimer-host, that use either hydrogen bonding interaction or hydrophobic complexation shows specific guest binding. The specific recognition sites on the interior of dendrimers are used for internalization of guest molecules. Reports of Newkome *et al.,* and Zimmermam *et al.,* [13, 38] showed that hydrogen bonding could occur on dendrimer interiors with similar binding constants to those observed in free solution phase.

The dendrimer type and generation number hardly play any role to complex a small guest. Other studies have reported that the electron rich dendrons increase the binding to the core element by classical electron donor–acceptor interaction, which involves electrostatic, polarization and dispersion forces.

Topological complexation: It has been proposed earlier that dendrimers with extremely densely packed end groups might permanently encapsulate guest molecules. It has been studied that the catenane and rotaxane formation may cause strong mechanical complexation of guest with host dendrimer which has been discussed later in this review [39].

Surface binding: Earlier it has been discussed in this review about the possibility of multiple and simultaneous complexation process on the surface of dendrimers possessing the peripheral groups. It was also found that the number of guest molecules bind per dendrimer decrease with increase in the generation number, presumably due to steric hindrance. An example of such binding is increasing in solubility of adamantly dendrimer linked to β-cyclodextrin. The surface binding of β-cyclodextrin increased the solubility of these PPI based dendrimers containing between 4 and 64 adamantyl end groups [40].

Covalent bonding: In such dendrimer – guest conjugates, the drug is attached through a covalent bond either directly or via linker/spacer to the surface groups of the dendrimer.

The loading of guest molecules (drugs) can be tuned by varying the generation number of the dendrimer and release of drug from dendrimers can be controlled by incorporating degradable linkages between the drug and dendrimers [3].

Chemistry of dendrimer self-assembly and self-organization: The dendritic structure contains three basic parts: the core, end groups and branched units connecting the core and periphery. So, there can be three strategies for dendrimer self-assembly. Self–assembly can be achieved by creating dendrons with a core unit, which is capable of recognizing itself or a ditopic or polytpoic core structure leading to spontaneous dendrimer formation.

Another approach can be the addition of layers or generations to the end group non-covalently. The above mentioned methods resemble convergent and divergent dendrimer synthesis [34, 39, 41]. The addition of layers or generations via recognition units on the branched monomer inside the dendrimer can be another approach which could be equivalent to grafting of dendrons onto specific reactive sites.

Hydrogen bond mediated self-assembly has been reported in some Frechet type dendrimers of higher generation, where stable hexameric aggregates have been formed by using bis (isophthalic acid) at the core. More stable hexamers were found with heterocycle containing two self-complementary hydrogen bonding sites.

Addition of dendrons containing catenanes, rotaxanes and pseudorotaxane crown were reported to complex ammonium ions and underwent self-assembly (**Figure 5**). Dendritic metallo-macromolecules are examples of self-assembly of dendrimers utilizing metal ions. Metal ligation steps are involved at the final assembly step to form the dendritic macromolecules [41, 42].

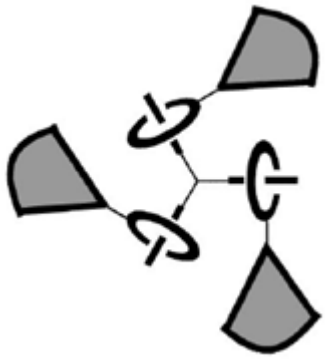

FIGURE 5: SCHEMATIC REPRESENTATION OF TRIDENDRON FORMED BY TRIPLE PSEUDOROTAXANE SELF-ASSEMBLY [39]

Self–organizing dendritic systems are those where long range ordering occurs due to some forces which are less specific and directional than those in self-assembly. So, it can be stated that the self-organization is guided more by nature than the investigator himself. Large dendrimers are having the property of forming liquid crystalline phase (LCP). The studies concluded that the self-organization phenomenon occurs at the interface and dendrimers can be used as building blocks for constructing mono- and multi- layers [34, 43].

Structure-property investigations suggest that molecular structure of the dendrons relates to self-assembled structures that ultimately organize into specific liquid crystalline phase. Interfacial organization is another mode of self-organization. The self-organization may produce rod like or cylindrical dendrimers, with some organization mediated by metal ions at an interface leading to ordered arrays of dendrimers.

Targeting techniques for Dendritic Polymers: The research findings on exploring the carrier properties of dendrimers revealed that these novel polymeric moieties are having the potential in particular to eliminate the difficulties in delivery of anticancer drugs, which are still a problem in the pharmaceutical world as these drugs are many a times effluxed from the cells by the p-glycoproteins producing phenomenon like multi-drug resistance and therapeutic failure. The covalently linked building blocks produce a more stable carrier system which can withstand physiological conditions more efficiently compared to liposomes and amphiphilic particles [44, 45, 46].

1. **Passive targeting technique:** The dendritic macromolecules carrying the therapeutic agents exploit the pathophysiological pattern of solid tumours, particularly their leaky vasculature to permeate and accumulate in the tumour tissue. This process is referred to as the enhanced permeability and retention (EPR) effect. The accumulation of these dendrimer based drug delivery system depends upon the size, molecular weight and surface charge of the dendrimers, which affect their residence time in the systemic environment, their transport across endothelial barrier and non-specific recognition and uptake by Reticuloendothelial System (RES) [47, 48, 49, 50].

   Many researchers have reported that increase in dendrimer size (molecular weight) exponentially increases the extravasation time and also lower generation dendrimers are quickly excreted in urine route, whereas higher generation dendrimers possess high hydrodynamic volume and have a limited renal secretion.

   The cationic dendrimers show high non-specific uptake by the RES in lungs and liver and have a higher net accumulation in each organ due to their electrostatic interaction with the negatively charged epithelial and endothelial cell surface. The attachment of PEG arms to the dendrimer surface increases their size and molecular weight, reducing their systemic clearance and improving biocompatibility [51, 52].

2. **Active targeting technique:** Cell-specific targeting ligands such as vitamins, carbohydrate residues, peptides or antibodies which selectively bind to the receptors expressed on the surface of cell are conjugated to polymer-drug couple. This targeting is particularly of great significance for cancer cell targeting [53, 54]. Binding of the ligands to the receptors expressed on the cancer cell surface triggers receptor mediated endocytosis and internalization of the whole conjugate into the cancer cell. Such system by-passes the non-specific uptake by the RES and hence increase in concentration of the system in the cancer cell.

Targeting ligands like Folic acid (FA) and Riboflavin are reported to be successfully delivered to tumour cells in lungs, breast and brain, where over expressed Folic acid receptors (FAR) are found [55, 56]. Peptide ligands like Neurotensin (NT) were reported to deliver drugs like Methotrexate to the cancer cell, particularly at colon, pancreas, prostate and lungs [57]. Targeting to the brain has been studied successfully by cross-linking with D-glucosamine ligands. These ligand conjugates were targeted to the GLUT-1 transporters which are highly expressed on the luminal side of the endothelial cells of the blood- brain barrier and glioma cells [58]. Similarly, ovarian carcinoma cells were reported to be targeted by the lectins, which are expressed on the surface of ovarian carcinoma cells, by a tetrameric avidin glycoprotein dendrimer conjugate [59].

Dendrimers can be used as vectors for delivery of genetic material into the nucleus [60, 61, 62]. These are having desirable properties to replace liposomes or genetically engineered viruses for this purpose. Polypropylene imine (PPI) and poly (amidoamine) are particularly getting more concern in this field. Cationic dendrimers are used to deliver negatively charged genetic material into the cell by forming a complex by electrostatic interaction. These cationic dendrimers form compact complexes with the DNA[63, 64, 65].

PAMAM dendrimers have terminal amino groups which interact with phosphate group of nucleic acid to form transfection complexes. Sialic acid coating over the dendrimers can be used for complexing influenza virus. The non-immunogenic nature of dendrimers offers additional suitability to serve the purpose [66].

Multifunctional dendrimers have emerged as potential candidate for targeted drug delivery system. Dendrons with different surface groups are synthesized by convergent methods. Targeting to the colon region is found to be advantageous because of lack of gastric enzymatic environment and long residence time. Anticancer drugs can be targeted to this site by using multifunctional dendrimers. Peptide [67, 68, 69, 70] and saccharide [71] conjugated dendrimers are currently getting more importance, because of their wide contribution in drug targeting, like improving of site specificity property, suitability for gene delivery and increasing cross-membrane capability of dendrimers [71]. Saccharide conjugated dendrimers are additionally having good water solubility and biocompatibility.

Effective targeting of these dendrimer based drug delivery systems can be achieved by the selection of a selective ligand and optimization of the ligand valency to tune the binding and dissociation rates of the targeted conjugates at the specific sites.

CONCLUSION: Over the last three decades there is a remarkable progress in the controlled polymerization and synthesis technique for obtaining a controlled dendritic structure with a large number of surface groups, which can be utilized for coupling biological motifs and drug moieties. The high drug loading capacity of the dendrimers aids to their suitability in drug delivery. PEGylation of dendrimers was proved to increase their aqueous solubility, stability and reduces the non- specific toxicities. Incorporation of pH sensitive linkers in dendrimer-drug conjugate allowed for specific drug release in the cell endosome.

The hydrophobic drugs can be incorporated in dendrimer voids to deliver them, however the release kinetics of the encapsulated drug remains a challenging task that depends on the size and hydrophobicity of drug molecule. Another noteworthy property of dendrimers is that, these are excellent building blocks for self- assembly and self-organization.

A new area of research in dendrimers is the development of dendrimer cluster, where several dendrimers are bound together through physical or chemical forces to form a multifunctional therapeutic system, which will open a new path for combination drug therapy which seems to be beneficial for treating diseases like cancer. However, successful targeting and understanding the kinetics of dissociation of host-guest complexes are still in infancy and need constant efforts.

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