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APPLICATION OF DENDRIMERS IN DRUG DELIVERY: A MULTIFACETED APPROACH

Biological Science

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ABSTRACT

Dendrimers are highly branched synthetic nano polymer, which have unique 3D macromolecules structures. Its unique branched tree like structure provides enough peripheral surface functionality and flexibility to attach or link desired molecules. The distinctive architectural design of dendrimers and other structural appearance have an immense effect on their other chemical and physical nature. High level of controlled design and construction of dendrimer in their shape, size, length of branch and their exterior surface monolayer functions distinguished by virtue of these specific features offer as most advantageous carriers in various biomedical and industrial applications. Dendrimers based targeted delivery is most emerging, particularly in the delivery of drugs and bio-macromolecules such DNA and siRNA for improving the index of therapeutic potential. This review briefly describes about the dendrimers and theirs types, synthetic strategies, properties and different functionalities with their area of utilization, applications in drug delivery as well as other biological deliverables.

KEYWORDS

Dendrimers, Nanocarrier, Surface Functionalities, Drug Delivery.

1.0 INTRODUCTION

Dendrimers are highly branched polymeric nano-carriers. They have attractive features with a well-defined structure including globular in shape, mono-dispersive in nature, large number of peripheral groups and incorporation of different functionalities (Vogtle 2009). Dendr imer term is originated from two Greek words; '*dendron*' and'*meros*' means and 'part' and attribute to the distinctive association of repetitive monomeric units.In 1978 Fritz Vogtle and their coworkers created the first dendrimers, polymers with a tree-like branching structure. They described a series of synthetic molecules by repetitive reactions of a central core with mono- and di-amines to generate large molecular cavities of polymeric branching units and named them as "Cascade molecules"(Buhleier E, 1978). In 1985 Donald A. Tomalia had synthesized first family of dendrimers and explained about the iterative combination of central ammonia core to ethylene diamineand fabricates a number of branched high molecular weight polymer named "starburst dendrimers" Tomalia DA, 1985. The highly branched three-dimensional structures of dendrimers consist a high precisionoutside edgesurface functional area and flexibility for enhanced drug delivery system (Nanjwade et al., 2009). Dendrimers are provide inter connection polymer science and guest host chemistry. They are very have emerging interest on guest host chemistry due to have advantage of their stepwise controlled synthesis and unique structure. Dendrimers are also most convincing molecules in the polymer science due to of theiriterative coupling pattern of mono-meres. One of the most interesting features of dendrimers is that occurrence of a excessive number of surface functional group by which the properties of these macromolecules can be functionalized without altering internal hierarchical order (Frechet, 2002).The exceptional features of dendrimers offers high degree of densely packed spherical structure regular branching, multivalency, and precise molecular weight, water solubility. These features of dendrimer clearly distinguish as versatile and most advantageous nanocarriers. This versatility has opened a wide scope of research by understanding the interactions taking place between the biological entities for example drug delivery, antineoplastic drug delivery, gene transfection, photodynamic therapy, photothermal therapy and neutron capture therapy (Agarwal et al., 2008; Ambade et al., 2005; C. Wu et al., 1994; Dufes et al., 2005; Hu et al., 2008; Konda et al., 2001; Nishiyama et al., 2009).Additionally, application of dendrimers is also being considered as a catalyst and organic light-emitting diodes (L. Brauge et al., 2006; Nlate et al., 2006). Interestingly, dendrimers with the amenable terminal functional groups can be surface engineered for various specific applications, e.g. enhancement of drug solubility and permeability, and targeted delivery particularly in the perspective of biomedical applications (S. Pushkar et al., 2006). In the past few years, dendrimershas been shown an emerging prospect in biomedical applications together with anticancer and diagnostic imaging therapies. The unique distinct structures of dendrimer make them the most up-to-date class of molecules for transport of drug delivery. A variety of drugs or molecules have very strong curative efficacy but limits their pharmaceutical applicationsowing totheir cytotoxicity, solubility, bioavailability and permeability.Dendrimershave an excellent capability to improve the solubility, bioavailability and permeability of drugs or molecules for optimization and can be used as nanocarrier in pharmaceutical applications. Modern advances in dendrimer chemistry may afford an opportunity to simplify and optimizing the synthesis of dendrimers for various applications with low cost and targeted delivery.

2.0 ADVANTAGES OF DENDRIMERS IN DRUG DELIVERY:

Dendrimers provides number of advantages in contrast of theother linearpolymers:

1. Dendrimers affords a structural consistency and monodispersity.
2. Dendrimers form a compactly dense ball like in solution. This lead immense effect on their rheological properties such as viscosity, density etc. Dendrimerhas lower viscosity than the other linear polymers.
3. The terminal groups of dendrimercould be modified to recognize particular receptor.In addition, the existence of reactive functional groups on the surface of the dendrimer may offer greater targeting efficiency.
4. The surface engineering and designing and modification dendrimer mimicking biological exo-receptors, substrates, inhibitors or co-factors.
5. Dendrimers may advances intracellular trafficking or drugs transport within the cell.
6. Dendrimer can entrap of variety of drug molecules in the internal void by the charge interaction or with the addition of different type of functional groups.
7. Dendrimers can release the drug by modified stimuli or response (pH change or irradiation).
8. Dendrimers have good biodegradability, limited toxicity and non-immunogenicity.
9. Lower generation anionic or neutral polar terminal surface groupsdendrimers hold great biocompatibility than the higher generation neutral apolar and cationic surface groups.
10. With addition of small functional groups or polyethylene glycol

(PEG) on cationic dendrimersurfaces, which may result non or low-immunogenic response.

11. Dendrimerexhibits pharmacokinetics properties having better colloidal, biological and shelf-stability.
12. Dendrimer can encapsulate the drug molecule into its cavity, from which the drug is slowly released, thus dendrimer can used to control/prolong the release of drug.
13. Dendrimers used as carrier of nucleic acids drugs by encapsulation or by covalent attachment method
14. Dendrimers have been used for drug delivery systems for many drugs such as anti-cancer, anti-tubercular as well as anti-viral by enhancing bioavailability especially sustained, controlled and targeted release of the drug.
15. Drug toxicity can be diminished by the reduction in the amount of drug conjugation or entrapment.
16. Cytoxicity of the dendrimer can be reduced by controlled synthesis.

3.0 ARCHITECTURE AND COMPOSITION OF DENDR IMERS:

Dendrimersvary from traditional polymers due to their hydrophilic outer surface and hydrophobic interior core, whichprovides unique structure and micelle like properties.Unique three dimensional structures and multi-valency of the dendrimersmay improve delivery of desired drug candidate(Patri, Majoros, & Baker, 2002). The periphery surface area, shape and size of dendrimer are theinterest ingf eature, which opens the wide scope for utilization in biomorphic/ biomimetic application. Their void interior and exterior surface provides a space to fit and fix drugs and other bioactive physically or by other various interactions to act as drug delivery vehicles(Bosman, Janssen, & Meijer, 1999).

Dendrimers composed with three distinguished architectural compo nents as shown in Figure 1.

1. An initiator core.
2. Interior layers (generations) composed of repeating units, radically attached to the interior core.
3. Exterior (terminal functionality) attached to the outermost interior generations.

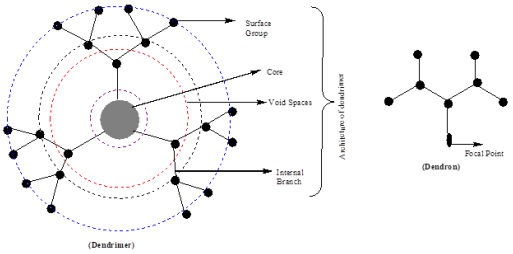

Figure 1. Schematic presentation of dendrimer (left) and a dendron (right)

The branched structural design of the dendrimer leads to a controlled increments in a molecular weight, size, and number of surface functional groups.As the generation of a dendrimer increases, its size, shape and number of surface functionality increases accordingly. Addition of generation allows its increasing size and shape of the dendrimerthat becomes more spherical and defined. Dendrimers all bonds come together to a focal point or central core unit. Due to a high efficacy of branching exterior dendrimers adopt a spherical globular shape. Dendrimer's surface group's functionality nature sturdily influenced the solubility. Polar solvents solubilize the dendrimers terminated hydrophilic groups, although non-polar solvents solubilize the hydrophobic end groups of dendrimers.The steric considerations contribute a globular shape of dendrimers, which can affect their capability to interact with adjoining molecules(Kitchens, El-Sayed, & Ghandehari, 2005; Tomalia DA, Naylor M, & III, 1990).

4.0 COMPONENTS OF A DENDRIMER STRUCTURE:

Dendrimer structure is defined by three main components which are core, shell and end group (Bosman et al., 1999; SC., 1997;Zeng & Zimmerman, 1997).

4.1 CORE

The structure of dendrimer begins with a central group of atoms, which is defined as core. The core affects thedendrimer 3D shape. Dendrimer central core element is denoted as generation “zero” or “G0”. Dendrimer synthesis expands outward from a multifunctional core molecule.Synthesis of first-generation of dendrimer begins with the core molecule that reacts with the monomer molecules consist with one reactive and two inactive groups intermediates. These interme diates were sometimes denoted as half-generations. Generation is ordinary for hyper branching of dendrimer when extending from the center core of the dendrimer towards the periphery, which resulted generation of homostructural layers between the focal points (branching points). When number of branching point increases from core towards the dendrimer periphery denoted as a generation number.For example, 4th generation is represented as a dendrimer possess four branching points starting from the center to the periphery and abbreviates simply as G4-dendrimer.During synthesis of the dendrimer as generation increases, it gets moderately more shielded off from the atmosphere by the dendritic chains and forms a compact core in central point. The center of the dendrimer provides protective microenvironment which may have exceptionally unusual properties as compared to the atmosphere or surrounding. For example water soluble dendrimers have been used to carry hydrophobic drugs in the bloodstream with an apolar interior region.

4.2 SHELL

The homostructural spatial segment of dendrimer shell between the branching points is called as “generation space”. The space between the last outer branching point and the outer layer is known as “outer shell”. The dendrimer interiors are generally mentioned as “inner shells”. The shell affects the host- guest / complexation properties of the dendrimers(U Boas, 2006).

4.3 END GROUP

The periphery of the dendrimer has the end groups, which holds functional recognition site for multiple interactions with biological receptors. For example, dendrimers having lactose or maltose sugar known as “Glycodendrimers”. As a result, several research groups have endeavored to construct well-defined macromolecules easily and displaying a large number of different types of ligands using dendrimers as carriers to achieve multivalent ligand-receptor interactions and utilize them for recognition and targeting to specific cells[1].

5.0 APPROACHES FOR SYNTHESIS OF DENDRIMERS:

In recent past various methods were developed to synthesize different types of dendrimers with versatile approached and chemical compositions(Medina & El-Sayed, 2009).Notably, Dendrimers construction is usually formed in an interactive series of reacting steps. An assembly of dendrimer has been associated many variations according to their generation. In synthesis of dendrimer, each supplementary interaction increases advanced generation of the dendrimer. At each step new layers develop a new 'generation' and it leads to doubling-up the number of end groups (or active sites). Therefore, the size, generation number and surface functional groups of dendrimerwere increased at each step. As a result the activity of dendrimer depends on these characters. As the dendrimer generation increases, the diameter of dendrimer increases linearly while the number of surface group increases exponentially. The synthesis allows almost entire control over the critical molecular design such as size, shape, branching length, surface functionality, flexibility, and topology of dendrimers which identifies unique structure and carrier for the application as they offered numerous chemistry, biology and medicinal applications(J. M. J. F. D. A. Tomalia, 2001). The choice of the growth reaction offers the way of branching should be introduced into the dendrimers. There are mainly three different methods including divergent growth method, convergent growth method and mixed growth method, which commonly were used for synthesis of the dendrimers. In the different methods, dendrimer was synthesized to different generation from a multifunctional core moiety.

5.1 DIVERGENT GROWTH METHOD

This method starts by a series of reactions called Michael reaction, which radiates out from central core and extend towards the surface with the number of branch points on a particular arm. The one reactive site successive liberated through to the first generation dendrimers. The first generation reactive site reacts with another monomer to give second generation(DA., 2004.). This process is reiterated until the desired size of thedendrimerwas obtained (Figure 2). Large scale synthesis or industrial scale dendrimerwere generally synthesized by

this approach. Since, addition of reactive monomers in every generation step and thus resulted molar mass of the dendrimerwould be doubled. The main problem associated in this process is side and incomplete reactions of the end groups that cause structural defects. This structural defect leads to some difficulties in the purification of the final product.

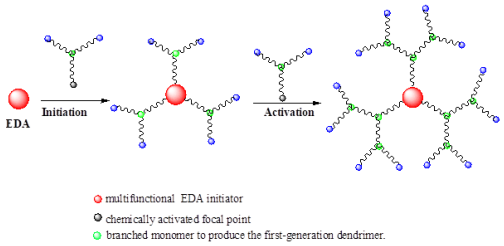

Figure 2. Schematic representative of divergent method for synthesis of dendrimers.It begins with a multifunctional initiator core (red) that reacts with the chemically activated focal point (black) of a branched monomer (green) to produce the first-generation dendrimer.Higher generations are synthesized by the iterative addition of the branched monomers, producing a complete dendrimer terminated with functional chemical groups (blue).

5.2 CONVERGENT GROWTH METHOD

This is another method which has been used for synthesis of the dendrimer. This was invented by Hawker and Frechet in 1990 (Hawker & Frechet, 1990). Synthesis of dendrimerby this method is two step processes, which initiate from the surface of dendrimer and progresses inwards (Figure 3). Unlike the divergent method applying of this approach product may easily purified and the finally structural defect free product could be obtained in each generation. This method is generally restricted to the building of dendrimers with advanced higher generation, but major hurdle is steric hindrance occurred when dendronswere attaching to the molecular level core. In this process number of functional reactive site generally gets very low (Klajnert & Bryszewska, 2001)

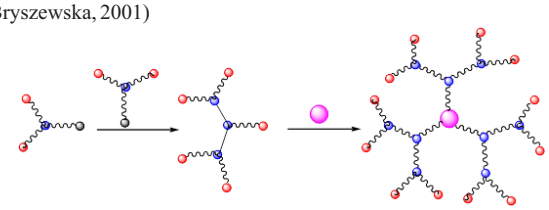

Figure 3.A Schematic drawing showing the convergent method for synthesis of dendrimer

5.2 MIXED GROWTH METHOD OR DOUBLE EXPONENTIAL METHOD

This is more advanced method for synthesis of the dendrimer and alike to linear polymer rapid growth technique. In this approach generally starting martial of the dendrimer(monomers)were prepared from the both divergent and convergent method (Figure 4). Strength of double exponential growth approach is associated with fast synthesis and dendrite fragment can be extended easily with either divergent or convergent growth. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings(Gillies & Frechet, 2005).

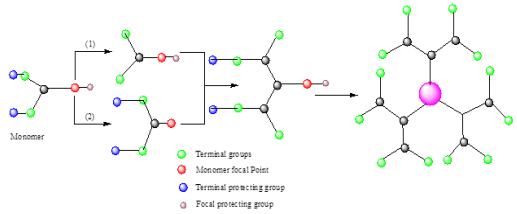

Figure 4.A Schematic representative of mixed growth method for synthesis of dendrimersUsing separate deprotection schemes, (1) the monomer's terminal groups (2) or the focal point are deprotected and coupled together to yield the dually protected dendron. Divergent dendron growth can then continue through deprotection of blue and iterative monomer coupling or the complete dendrimer can be formed by deprotection of brown and coupling of the dendron focal point (red) to a multifunctional core followed by deprotection of blue.

6.0 FACTORS AFFECTING DENDRIMER PROPERTIES:

6.1 EFFECT OF PH

Dendrimers have amine functional group at the surface as well as positively charge interior tertiary amines were present in both (Amine terminated PAMAM and PPI dendrimers). At low pH (less than 4), the inner void is receiving more "void cavity" accordingly increase the generation or core size of the dendrimer resulting electrostatic repulsion between two amine surface positive and interior positive tertiary amine that leads to extended conformation. The recent findings highlighted that although the back-folding occurs at neutral pH and only primary amines were protonated, which may be outcome of hydrogen bonding between the uncharged tertiary amines in the interior and the positively charged surface amines. It decreases generation or core size of dendrimer. However, at higher pH (More than 10) protonation does not occur, the dendrimer become a more spherical (globular) in shape when the charge of the molecule becomes neutral. In this case the repulsive forces reaches neutrality comprises the dendrimer arms and the surface groups. So, there is further increase in the size of the dendrimers because of the conformation hold a higher degree of back-folding. As a consequence of the weak "inter-dendron" repulsive forces, similar developments have been also observed for PPI dendrimer(Gupta, Agashe, & Jain, 2007; van Hest, Delnoye, Baars, van Genderen, & Meijer, 1995;Wang & Imae, 2004).

6.2 EFFECT OF SOLVENT

The effect of the solvent is an extremely noteworthy feature to dissolve the dendrimerand examine the conformational status. Intra-molecular interactions between the dendrimer segments and back-folding poorly favor in non-polar solvent. It was observed that intermolecular interaction highest at low generation due to being more flexible as compared to the higher generation dendrimer.The lower generation of the dendrimer has more salvation ascompared to the higher generations that may be a consequence of the more open structure,solvent molecules penetrate more easilyinto the interior of the lower generation dendrimer. It results in to swelling of the dendrimer for example G5 dendrimer swell 33% compared to untreated with solvent(Maiti, Ça ın, Lin, & Goddard, 2005). Polar aprotic solvents, like acetonitrile, dimethylformamide, dimethyl sulfoxide dissolves the dendrimer arms and induces the dendrimer higher molecular mass on surface leads to a shrink in hydro dynamical volume owing to of improved intra-molecular - interactions and was most evident for the G4 dendrimers. An absolute conformation of dendrimer (PPI and PAMAM) is the outcome of hydrogen bonding between the weakly acidic solvent (polar aprotic solvent like chloroform), which acts as a hydrogen donor for amines. Experimentally as well as theoretically recent study shows that polar dendrimer (amino terminated PPI and PAMAM) has propensity of back-folding, but in apolar aprotic ("poor") solvents, which induce higher molecular surface densities towards the central core region. Higher density on the dendrimer surface is induced by polar solvents which helps to dissolve the arms of the dendrimer(Tripathy1 & Das, 2013).

6.3EFFECT OF SALT

Salt concentration affects the properties of the dendrimers. Molecular simulation study suggested that an extended conformation in order to diminish charge repulsion in their structure due to low salt conditions, low ionic strength, which has repulsive forces between the charged dendrimer. However, at high salt conditions, ionic strength has high impact in the charged dendrimer and favors a high degree of shrink structure of dendrimer as similar as noticed in increasing pH or poor solvation(Gupta et al., 2007).

6.4EFFECT OF CONCENTRATION

The molecular study revealed that the density and conformation of the dendrimer is not only influenced by solvents, salts, pH or protons, but it is also being affected by the concentration that may influence density and conformational structure of the dendrimers. For e.g. PPI dendrimers (G4, G5) in a methanol (polar solvent) showed that upon increasing concentration, dendrimers conformation start compacted. This molecular contraction may reduce the repulsive forces between the dendrimer molecules and allow to compact intermolecular packing(Topp, Bauer, Tomalia, & Amis, 1999).

7.0 DENDRIMERS AS A CARRIER FOR DRUG DELIVERY

Dendrimer are a new class of molecule which can be used for improved drug delivery at nano-scale. Dendrimers are appealing choice for drug delivery due to its unique supra-molecular and interfacial characteristic and it has ability to increase solubility, permeability of drug molecules, high drug loading capacity, good biodegradability and

chemically adjustable peripheral functional groups also helps in design of controlled release formulations(Patri et al., 2002). The pharmacokinetics value of the drug can be improvedwhen toxicity of the drug may be reduced. This is possible when vehicle could be developed that selectively delivers the drug at the target site. Dendrimers are one the suitable carrier for drug delivery or control release of the drug because of certain structural advantages. There are most conventional techniques of dendrimer based drug delivery which includes first encapsulation of drugs where drug is non-covalentlyor physically trap in the interior of the dendrimer and second dendrimer-drug conjugates; covalently or electro-statically conjugated to dendrimer's surface.

7.1 ENCAPSULATION OF THE DRUG

The encapsulation of a molecule inside a dendrimer was first reported by Meijer and coworkers 1994(Jansen, de Brabander-van den Berg, & Meijer, 1994). The compact and branched structure of the dendritic favor to entrap poorly soluble drug molecules inside the core or linking outside with branches of a dendrimermay leads enhance stability of the drug, bioavailability and controlled release (Medina & El-Sayed, 2009). Therefore dendrimers attract interesting drug delivery carrier for various applications. Several reports highlighted numerous extremely active drug molecules could not be used clinically due to poor water solubility and showing high toxicity because they have been used at higher concentration for effective response(Kawabata, Wada, Nakatani, Yamada, & Onoue, 2011; Savjani, Gajjar, & Savjani, 2012). Hence, method of encapsulation of drugs in dendrimersmay offer an enormous potential for drug delivery system. Recent advances in dendrimer chemistry encapsulation method of anticancer drugs like camphothecin, 6-mercaptopurin and methotrexate etc into the interior of dendrimersfavor selective targeting of the malignant tissue(Cheng, Li, & Xu, 2008; Luo & Prestwich, 2002; Morgan et al., 2006; Myc et al., 2008). Interestingly, encapsulation of 5FU with the dendrimer showed increased permeability in the skin due to longer lag time and lower diffusion coefficient(Dijkgraaf et al., 2007).Enhanced aqueous solubility of paclitaxel was achieved with poly (glycerol) dendrimer formulations(Ooya, Lee, & Park, 2004). Therefore; encapsulation of small and low molecular weight drug may protect from the degradation andslow release from the dendrimers can be applicablein drug delivery system and could be useful for therapeutic interventions.

7.2 COVALENT CONJUGATION

Covalent conjugation of the dendrimers is an alternative and interesting approach to attach the drug molecules through a covalent bond either directly or using linker or spacer to the surface groups inthedendrimer(Kaminskas, McLeod, Porter, & Boyd, 2012). The occurrence of masses of functional groups on the exterior of dendrimers makes them appropriate for the covalent conjugation of number of same or different and multiple drugs molecule with appropriate functional groups. This is the key point of covalent attachment of drug molecule with core scaffold by the different bio-conjugation reaction. On each dendrimer molecule multiple drug molecules and targeting ligands can be attached and these therapeutic molecules could be released by the degradable linkage between the drug and dendrimer(Boas & Heegaard, 2004). Generally most of drugs were attached to the dendrimers by covalent linkages. The chemical linkages include; ester, carbamate and hydrazone are pH- sensitive linkers and cleaved by acidic environment. A variety of enzymatic degradation required for their own degradation mechanism to separate the drug molecule from the carrier vehicle dendrimers such as disulfide linkage can be reduced by glutathione within the cytosol. Amide linkage its robust type linkage preferably not used in conjugation due to its stability and slow release of drug. Owing to the properties of multivalency and high surface group to molecular volume of dendrimers, it has been conjugated with several biological molecules such as drugs, antibodies, sugar moieties and lipids. One of the best example can consider here as Paclitaxel was conjugated with G4-PAMAM dendrimer for drug delivery resulted in significantly aqueous solubility improved from 0.3 µg/ml to 3.2 mg/ml and the IC_{50}value of the conjugated drug was decreased more than 10-folds as compared to the free Paclitaxel(Khandare et al., 2006). Another well know anti-cancer drug Cisplatin, which has been frequently used in cancer therapy. This drug has major hurdle as its limited aqueous solubility and toxicity, but after conjugation of cisplatin with PAMAM dendrimers shows enhanced solubility, decreased systemic toxicity and selective accumulation in solid tumors. Recent report demonstrate thatdendrimer-platinum complex has been also found effective and less toxic as compared to thecisplatin, which has been used in the treatment of subcutaneous B16F10 melanoma(Malik, Evagorou, & Duncan, 1999). In a study carried out by Baker's group, G5 PAMAM dendrimer was conjugated with folic acid and methotrexate (MTX) and this conjugate was found to specifically kill KB cells that overexpress folate receptors by intracellular delivery of the drug through receptor-mediated endocytosis. Moreover, the anti-proliferative effect was reduced when the folate receptors were blocked or down regulated(Patri, Kukowska-Latallo, & Baker, 2005). Therefore, conjugation chemistry of dendrimer may offer effective drug delivery for treatment of cancer. Currently the novel dendrimer structures are being synthesized to explore the control of release kinetics for drug delivery.

7.3 Electrostatic Conjugation

Dendrimer offers a remarkable opportunity to conjugateionizable drugs. The presence ofionizable groups(amino and carboxyl) on the surface of the dendrimers, which enhances the solubility of hydrophobic drugs. In recent pastnon-steroidal anti-inflammatory drugs those have carboxyl groups like i.e. ibuprofen, ketoprofen, diflunisal, naproxen and indomethacin have been attached with dendrimers by electrostatic interactions(Sebestik, Niederhafner, & Jezek, 2011). Ibuprofen predominantly conjugated with PAMAM dendrimers due to the ionic interaction between the amine end groups of dendrimer and the carboxyl group of weakly acidic drug ibuprofen. It has been noticed that conjugation of ibuprofen with G4 PAMAMdendrimerssignificantly enhances drug solubility at pH 10.5, where 40molecules of ibuprofen were interacted with G4 PAMAM dendrimer(Garg, Singh, Arora, & Murthy, 2011).

8.0 TYPES OF DENDRIMER AND THEIR APPLICATIONS IN DRUG DELIVERY:

In recent pastdendrimershave been received a major attention for various biological applications due to their unique branched structure, symmetrical shapes peripheral functionalities and monodispersity. Here we have briefly described different types of dendrimersalong with their applications.

8.1 PAMAM DENDRIMER

Among all the dendrimers, Poly-amidoamine (PAMAM) Dendrimer is the most extensively studied and interesting for all prevailing applications of dendrimers. Based on architecture, Dendrimer allows unique new class of synthetic nanostructures, accurate organizes of size, shape and adjustable functional groups which are interesting for many biological applications(Maiti, Ça ın, Wang, & Goddard, 2004). An additional wonderful quality is their exact mimicry of globular proteins. Due to their outstanding systematic, dimensional length and other biomimetic properties, so they are frequently identified as 'artificial proteins'(Chen, Banaszak Holl, Orr, Majoros, & Clarkson, 2003). PAMAM dendrimers contain an ethylenediamine [EDA] or ammonia inner core with amide and amine linkages alternating between carbon spacers along the branches and are usually terminated with amines or esters. For amidoamine repeating units' ammonia and ethylenediamine (EDA) molecule provides three and four possible binding sites. Two new branches may be attached to each primary amino group's present on the surface of the molecule. The PAMAM dendrimers having amino groups and carboxylic acid groups at terminal or surface of dendrimer are acknowledged as full generation dendrimers and half-generation dendrimers. PAMAM dendrimers are commercially available from generations 0 – 10 (G0–G10), having properties of a wide number of outermost groups (4 to 4096), functions of end group (e.g. amine, carboxylic acid, hydroxyl) and molecular weights (657 to 935,000 g/mol)(Wolinsky & Grinstaff, 2008). Because of above mentioned availability a numbers of experiments and studies have been performed on PAMAM dendrimer modification. For the synthesis of PAMAM dendrimers ammonia or ethylenediaminehas been used as initiator core reagent by applying divergent growth method. PAMAM dendrimer involves two successive steps in synthesis include first the primary amine (EDA) added to methyl acrylate through Michael addition resulting tetraester formed followed by amidation , with EDA(D. A. Tomalia et al., 1986). The half generation dendrimer having ester terminal group designated, 0.5 generation, this is formed during Michael reaction in the presence of methanol solvent. To produces complete amine terminated full generation dendrimers formed by amidation reaction of ester terminated dendrimers with addition ofethylenediamine in methanol. The duplication Michael reaction and amidation process leads to higher dendrimer generations (Figure 5). Most of the PAMAM dendrimers with modified surface are known to have non-

immunogenic property andwater solubleas well as their terminal modifiable amine functional groups which have capability to bind with several target molecules(Liang, Narayanasamy, Rapp, Schinazi, & Chu, 2006). PAMAM dendrimer acquire void internal cavities, where drug molecules can be encapsulated(Kojima, Kono, Maruyama, & Takagishi, 2000). PAMAM dendrimer conjugates also used for delivering drug and DNA. PAMAM dendrimers have shown promise for biomedical applications because they (1) can be easily conjugated or entrapped with targeting molecules, imaging molecules, and drugs, (2) have high water solubility and definite chemical structures, (3) are biocompatible and non-immunogenic, (4) have rapid renal clearance from the blood through the kidneys due to might be feasible because of their small size (< 5 nm) and exhibits minimum cytotoxicity up to generation 5.0(Liu & Frechet, 1999; Malik et al., 2000). Therefore, PAMAM dendrimersare quite interesting and may be unique tools for drug delivery system.

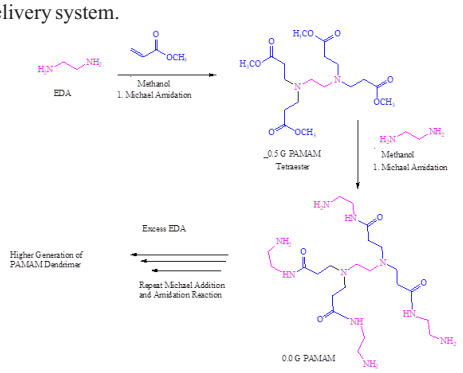

Figure 5.Synthetic scheme of PAMAM dendrimer.

8.1 PAMAMOS DENDRIMER

PAMAMOS [Poly(amidoamine-organosilicon)] is unique new family of first commercial silicon containing PetarDvornic and colleagues were first discovered PAMAMOS dendrimers at the Michigan Molecular Institute in the 1910(Dvornic, 2006). PAMAMOS are upright unimolecular micelles having hydrophobic organosilicon outer surface and hydrophilic, nucleophilic PAMAM inner layer and it is remarkably valuable originator for the formation of honeycombed like network with interior and OS domains exterior(Dvornic, Bubeck, Reeves, Li, & Hoffman, 2005). The formation of such networks is illustrated in (Figure 6). The organization of PAMAMOS dendrimer is honeycomb like networks have capability to interact and trap a variety of guest species with a nanoscopic topological precision suggest nano-lithography, electronics, photonics, magnetic, chemical catalysis, biomedical and pharmaceutical areas, sensing, protection, and decontamination, surface modification unique potentials for numerous mentioned applications.

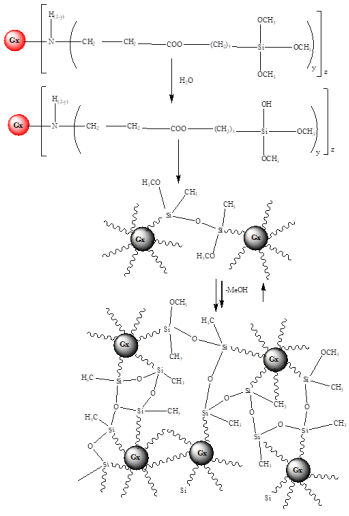

Figure 6.Schematic presentation of honeycomb-like PAMAMOS dendrimer networks.

8.3 PPI DENDRIMER

Poly(propylene imine) dendrimers have been abbreviated simply as PPI-dendrimers PPI-dendrimers describing the propylamine spacer moieties in place of amido amine in the PAMAM dendrimer which was synthesized by Vogtle and co-workers in 1978(Buhleier, Wehner, & VÖGtle, 1978). These dendrimers having usually poly-alkyl amines branches and primary amines at the surface groups; however the innner core of dendrimer consist a number of tertiary tris-propylene amines. The core is composed of ethylenediamine and the exterior contains the outmost propyleneimine chain. PPI dendrimer also been called as Astramoldendrimers or as DAB-Am-x dendrimers. DAB abbreviated for the diaminobutane core, where x was denoted for 4, 8, 16, 32 or 64 number of primary amine end groups which are associated with the numbers generations 1, 2, 3, 4 or 5, respectively. Commercially PPI dendrimers are also available up to G5 as Astramol^{TM}.

A synthetic scheme for the synthesis of PPI dendrimershas been shown in (Figure 7). It starts with the double Michael addition of acrylonitrile to ethylediamine core repetitively followed by catalyzed hydro genation of terminal nitrile groups. This progression results in a replication of end groups' number at each generation step. Since the addition of propyleneimine layer each branches of PPI dendrimer scaffold doubles the amino substituent on the surface, hence the steric hindrance will be also enhanced considerably. Therefore, after certain generation the reaction will stop for the dendrimer synthesis. So far, the 5th generation (PPI-5) is the highest generation of PPI dendrimer has been synthesized(Meijer). PPI dendrimers has found widespread applications in material and biological science(Richter-Egger, Tesfai, & Tucker, 2001). These dendrimers have been extensively investigated for their potential as catalysts. Crooks et al. reported the synthesis of PPI dendrimer encapsulating metal particles, and the use of them as homogeneous catalysts for hydrogenation(Crooks, Zhao, Sun, Chechik, & Yeung, 2001). PPI dendrimers apart from solubilisation of weakly acidic and weakly basic drugs Indomethacin and Famotidine, respectively but also used to solubilized drugs like Amphotericin B, which is amphoteric in character(Gupta et al., 2007).

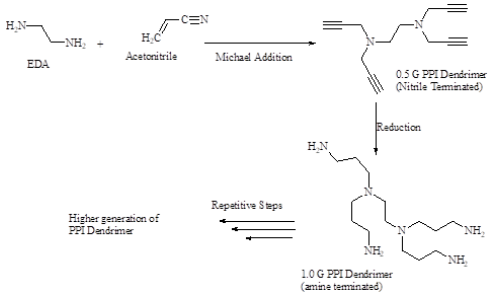

Figure 7.Synthetic scheme of PPI dendrimer.

8.4GLYCODENDRIMER

The term glycodendrimer was described as biologically relevant sugar residues linked to dendritic scaffolds. The first glycodendrimer was reported by Roy et al in 1996(Roy, 1996).They can be categorized in to three groups including carbohydrate-coated, carbohydrate centered and fully carbohydrate-based dendrimers(Lundquist & Toone, 2002). Carbohydrate on the cell surfaces plays important roles in the living systems. Thus Glycopolymers exhibits larger multivalent effect as compared to other molecules and provide wide range of application in biomolecules recognition. Although, amino terminated (PAMAM and PPI) dendrimers modified with glycosyl derivatives which have been widely used(Singh, Renaudet, Defrancq, & Dumy, 2005). There are numerous examples of carbohydrate based dendrimers synthesized via native glycosidic linkages, peptide coupling reactions, or reductive amination(Gray, 1978; Hahn, 1996; Sadalapure & Lindhorst, 2000;Turnbull, Pease, & Stoddart, 2000). Glycodendrimers have been used as protein–carbohydrate interactions and intracellular recognition of pathogen for several biological applications(Yoshiko Miura, 2013).In glycodendrimers accessibility of the sugars is an imperative key point which is efficiently used to estimate protein–carbohydrate interactions. Other applications of glycodendrimers have been suggested to be used as a carrier in such as incorporation into analytical devices, gel formulation, targeting of MRI contrast agents, drugs and gene delivery systems for medical application (Li, Cheng, & Xu, 2007).

8.5. PEPTIDEDENDRIMER

Peptide dendrimers are thoroughly branched macromolecules that include amino acids or peptides on the surface or amino acids or peptides on central core of the dendrimer. Peptide dendrimers can be

synthesized using either divergent or convergent approach. This dendrimer can be separated into three different classes. Foremost class of peptide dendrimers contains peptide only on the surface. The next class completely amino acids used in peptide dendrimer. The third category having non-peptide branching units dendrimers utilizing amino acids in the branching core and surface functional groups(Sadler & Tam, 2002).Peptide dendrimers have wide range of biological application includes surfactants in the industry, immunogens, protein mimics and carrier for drug delivery as well as gene and vaccine delivery(Boas, Sontjens, Jensen, Christensen, & Meijer, 2002; Sadler & Tam, 2002). Moreover peptide dendrimers have applications mostly in contrast agents like magnetic resonance angiography (MRA), magnetic resonance imaging (MRI), fluorogenic imaging and serodiagnosis(Crespo et al., 2005).

8.6TECTODENDRIMERS

Core–shell tecto-dendrimers or tectodendrimers have Controlled structure covalent polymers are synthesized by convergent method. They are a major subclass of poly (dendrimers) or megamers consist of a dendrimer core surrounded by a shell of lower- generation dendrimers (Figure 8). This class of central dendrimer attached symmetrically with multiple dendrimers at its circumference seizes potential for multidrug delivery and environmental remediation applications. The core of this dendrimers is surrounded by other dendrimers offers various functionalities for specific function therapy and diagnostics(Welch & Welch, 2009).

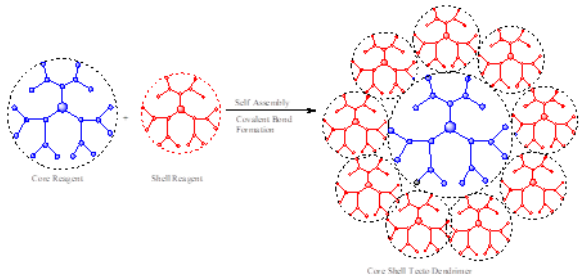

Figure 8.Synthetic scheme of saturated core-shell tectodendrimer.

8.7HYBRIDDENDRIMERS

Grouping of linear polymers and dendritic in hybrid block or graft copolymer forms. Zero-generation of polyethyleneiminedendrimers peripheral amines complete mono functionalization offer structurally varied self-organized lattices that are not easily changeable from other tailored dendritic structures (Percec et al., 2008). Hybrid dendrimers provide an attractive tool for removingpollutants from water due to their interior cavities and their ease of formation(Voit & Lederer, 2009). This type of dendrimers have accessibility to modifying surface functionality with stearate functional groups and have optical properties this an attractive application led to materials excellent solubility and film forming ability(Martinez-Ferrero et al., 2008).

8.8MICELLERDENDRIMERS

Specially designed micelle-like behavior in dendrimers is because of hydrophobic core and hydrophilic outer layer surface have shown to demonstrate and can also used to soluble hydrophobic molecules. Newkome reported use of dendrimers as unimolecular micelles(Liu, Kono, & Frechet, 2000; Newkome, Yao, Baker, & Gupta, 1985) . Unimolecular micelles are static and maintain their cohesion regardless of concentration. Whereas, conventional micelles are thermodynamic aggregates of amphiphilic molecules and are dynamic congregation of small molecules. Dendrimers hydrophilic (polar) terminal groups alteration with hydrophobic (non-polar) alkyl chains leads to the formation of reversed unimolecular dendritic micelles capable of extracting and concentrating polar molecules from their solution in non polar solvents (Fréchet, 2001).

8.9FRECHET TYPE DENDRIMERS

Hawker and Frechet were introduced this type of dendrimer, which is based on poly-benzyl ether hyper branched structure and synthesized by convergent method in that they assembled polyaryl ether scaffolds from the outside inwards (Frechet, 2002). At surface of Frechet type dendrimers have carboxylic acid (polar groups), so dendrimer behave as unimolecular micelle, probably due to the π-π interactions it has high capacity to soluble aromatic compounds, between phenyl rings in the scaffold and guest molecules. The Frechetdendrimers was also recognized as potential use of a solubilizing agent (Inoue, 2000).

9.CONCLUSION

The unique branched structure of the dendrimers has enormous potential to draw various biological applications. In the recent past dendrimersowing the attention to biologist and chemist for bridging the link for drug delivery and conceptualized forother various biological applications. Dendrimersacquire excellent structural features, such as high branching, nano size, multivalency, globular structure and well defined molecular weight, there by offering new scaffolds for drug delivery. It has greater flexibility in design. High control over the branching length, shape and size allows modification according to the delivery system, In this respect, the highly controllable features such as their size, shape, and surface functionality so these can serve as the ideal carrier for drug and various other applications. The large number of drugs is being developed today continuously but the problems related with those drugs are poor solubility, bioavailability and permeability. These problems associated with the drug can be overcome with the use of dendrimer for optimizing drug delivery system. Also the problem of biocompatibility and toxicity can be overcome by careful surface engineering. Development and recent successes in literature indicates that simplifying and optimizing the synthesis of dendrimers provides a cost effective synthesis methodology. Also as research progresses thus opening the, newer way for dendrimers will emerge and the future should witness an increasing number of commercialized dendrimer based drug delivery systems. Thus dendrimersmay provide further impetus to design, synthesize, and evaluate dendritic polymers for use in pharmaceutical application in drug delivery and translate at the clinical level.

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