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Dendritic Polymer for Drug Delivery Applications

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Abstract

Over the past 20 years, hyperbranched polymers have received much attention due to their unique chemical and physical properties as well as their potential applications in coatings, additives, drug and gene delivery, macromolecular building blocks, nanotechnology, and supramolecular science. Dendrimers are synthetic, highly branched, mono-disperse macromolecules of nanometer dimensions. The high degree of surface functionality, versatility and the unique properties like uniform size, high degree of branching, multivalency, water solubility, well defined molecular weight and also the available internal cavities. The ability of this macromolecule to construct a definite architectural design of dendrimers with respect to size and shape, length of branching, density, and its well defined molecular structure and segmented spherical construction has opened a wide area of research by understanding the interactions taking place between the biological entities. The impact of dendrimer applications on biomedical field as demonstrated in this review; shows major potential and high hopes for the future of dendrimers.

Keywords: *Dendritic Polymer, Chitosan, Drug delivery, Medical applications*

1. Introduction

Polymers are a large class of materials consisting of many small molecules that can be linked together to form long chains, thus they are known as macromolecules (Callister,2000).These macromolecules can be classified into three types: 1) linear polymers, where the molecules form long chains without branches or cross-linked structures, 2) branched polymers which consist of branched molecules, covalently attached to the main chain and 3) cross-linked polymers, which have monomers of one chain covalently bonded with monomers of other chain (Callister,2000).

2. Dendritic polymers

Dendritic polymers which refers to dendrimers and hyperbranched polymers, are highly branched macromolecules with a three dimensional dendritic architecture (Pushkar *et al*, 2006) (Muhammad *et al*, 2010). Dendrimers are the stepwise organic synthesis approach to branch-on-branch structures. Ideally, dendrimers are spherical, defect-free and perfectly monodisperse compounds. Dendrimer synthesis, however, is usually based on tedious multistep protocols. Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the required size. Dendrimers consists of three components: the core or focal point, interior layers/repetitive branch units or generations (G) which formed the dendritic units and terminal functionality at the exterior of the architecture (**Fig. 1**) (Turk *et al*, 2007).

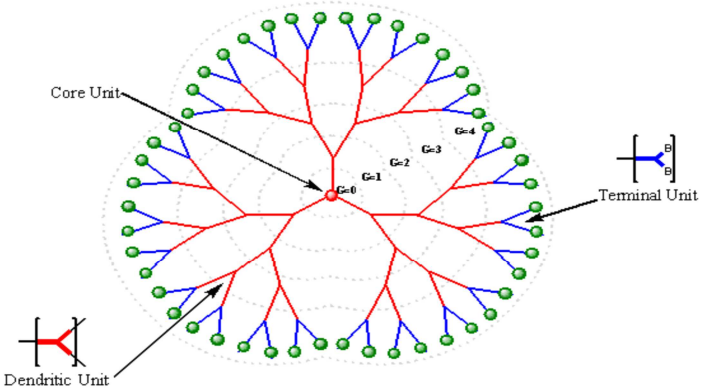

Fig.1: The architecture of dendrimer (Turk *et al*, 2007)

A second class of branched polymers is the hyperbranched polymers. In contrast to dendrimers, hyperbranched polymers are neither defect-free nor perfectly monodispersed. These polymers consist of the core, fully reacted (dendritic) and completely unreacted (linear) units and terminal units (**Fig. 2**). Hyperbranched polymers, however, are typically obtained in a one-pot reaction and as a result can be easily prepared in large quantities (Voit *et al*, 2005) (Haag *et al*,2000) (Indah *et al* ,2010) (Sunder *et al*, 1999).

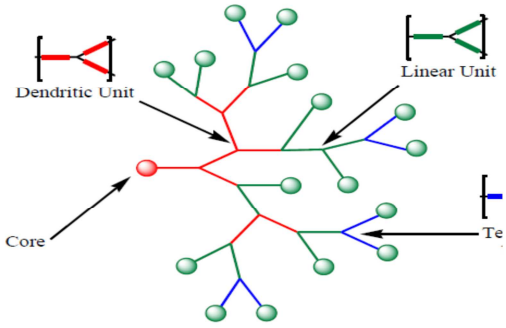

Fig. 2: Structure of hyperbranched polymers (Turk et al, 2007)

2.1. Synthesis of dendritic polymers

2.2. Synthesis of dendrimers

Dendrimers are a relatively new class of macromolecules that have a three dimensional structure with a series of layered branches regularly extending from a central core. Dendrimers usually consist of three main components : a multifunctional core, branch units and surface functional groups. Two methods that have been developed to synthesise dendrimers: the divergent approaches initiated (Egon *et al*, 1978) and further applied by Newkome (Newkome *et al*, 1985) and Tomalia (Tomalia *et al*, 1986) and the convergent method introduced by Hawker and Frachet (Hawker *et al*, 1990) and also by Miller and Neenan (Miller *et al*, 1990).

2.2.1. Divergent approach

The divergent method (**Fig. 3**) involves a stepwise layer by layer approach, which the dendrimer grows from a polyfunction core and builds up the molecule towards the periphery by the stepwise addition of successive layers of building blocks. Each of these layers is called a 'generation'. The first generation of a dendrimer is formed by attaching the branched unit to a focal core. For the second and subsequent generations, the surface functional group must react with the successive layers of building blocks. This reaction is repeated until the desired number of generations is obtained (Konkolewicz *et al*, 2011).

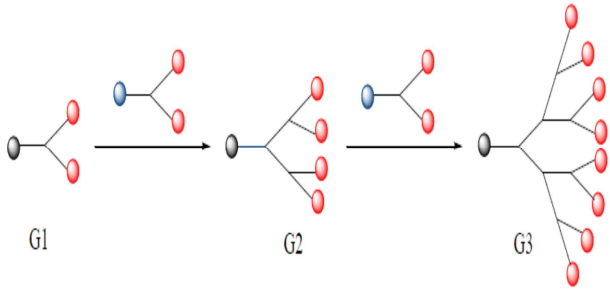

Fig. 3: **Schematic of divergent synthesis (Turk *et al*, 2007)**

2.2.2. Convergent approach

The second method, shown in **Fig. 4** an alternative method of synthesizing dendrimers. This alternative method is used to produce a more controllable dendritic architecture. The formation of the dendrimer begins at the surface functionalities of a dendrimer molecule and proceeds inwards by a step addition of branching monomers, followed by the final attachment of each branched dendritic subunit to the core (Matthews *et al*, 1998) (Miller *et al*, 1992).

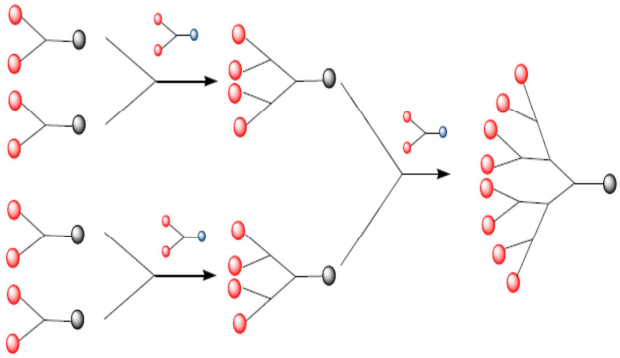

Fig. 4: Schematic of convergent synthesis (Turk *et al*, 2007)

2.2.3. Synthesis of hyperbranched polymers

Hyperbranched polymers, gained great attention after Florys in 1952 highlighted the polymerisation of ABn monomers (where n ≥ 2) to generate highly branched soluble polymers. Hyperbranched polymers with similar properties can be easily synthesized via one-step reactions and therefore represent economically promising products for large-scale industrial applications. Unlike dendrimers, these hyperbranched polymers are polydisperse systems both in terms of their molecular weight characteristics and their branching factors. (Yates *et al*, 2004)(Voit *et al*, 2000). The general synthesis of hyperbranched polymers can be divided into three specific categories: (i) step-growth polycondensation of ABn and A2 + B3 monomers, (ii) self-condensing vinyl polymerisation of AB* monomers and (iii)

multi branching ring-opening polymerisation of latent ABn monomers (Jikei *et al*, 2001).

2.2.4. Step-growth polycondensation

Step-growth polycondensation of ABn (where n ≥ 2) is extensively used to synthesise hyperbranched polymers (**Fig. 5**). The branching unit of these hyperbranched polymers is produced when each function of B from one molecule reacts with a function of A from another molecule. AB2 type monomers are used because of their ease of preparation. A vast range of hyperbranched polymers are produced using these techniques, including polyphenylenes, polyesters, polyethers and polyamides (Suzuki *et al*, 1992).Other types of monomers such as AB3, AB4 and AB6 are also used to synthesise polyesters and polysiloxanes.

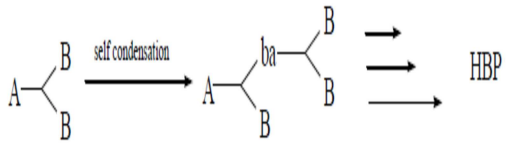

Fig. 5: **Step-growth polycondensation**

2.2.5. Self-condensing vinyl polymerisation

The second technique uses self-condensing vinyl polymerisation and was introduced by Frechet in 1995 which involves the use of one vinyl group and one initiating moiety (AB* monomers) to produce hyperbranched polymers (**Fig. 6**). The activated species can be radical, a cation or a carbanion. In this process, it is preferable to use living or controlled polymerisation (SCVP) to avoid cross-linking reactions and gelation caused by dimerisation or chain transfer reactions.Hyperbranched polystyrenes and poly (methacrylates) have been successfully synthesised by using this method (Yates *et al* ,2004).

2.2.6. Ring-opening polymerisation

The last strategy used to produce hyperbranched polymers is the ring-opening polymerisation technique which was introduced by Suzuki in 1992 (**Fig. 7**). The terminal function of a polymer acts as a reactive centre, where further cyclic monomers join to form a larger polymer chain through ionic propagation. Each additional monomer step produces another reactive centre. This method is used to produce hyperbranched polymers such as polyamines, polyethers and polyesters (Sunder *et al*, 1999)(Liu *et al*, 1999).

3. Dendrimers in drug delivery

Dendrimers are synthetic, highly branched, spherical, mono-disperse macromolecules of nanometer dimensions, prepared by the iterative synthetic methodology. Since the pioneering work of Tomalia *et al.* and Newkome *et al.* on dendrimer synthesis in the early 1980s, several research groups have contributed both synthetic methodology and specific applications for this field. There is a continuing effort to improve the efficiency and lessen the cost of synthesizing these macromolecules. Further investigations also are examining the specific physical and chemical properties of dendrimers and, although there are many factors that remain unknown, potential applications for dendrimers are now forthcoming. These macromolecules have uniform size and are mono-dispersed. They also have modifiable surface functionality as well as internal cavities (Jansen *et al*, 1994). These characteristics, along with water solubility, are some of the features that make them attractive for biological and drug-delivery applications (Esfand *et al*, 2001) (Liu *et al*,1999). In fact, much of the current work in this field is focused on the characteristics of dendrimer-based devices *in vivo*.

Polymeric micelles provide a model of sorts for dendrimermediated drug delivery. In polymeric micelles, the drug molecules can be trapped in the inner hydrophobic core while the outer shell is hydrophilic and soluble in aqueous media. However, below a critical micelle concentration, the polymeric aggregates dissociate into free chains, leading to the sudden release of the drug. Newkome *et al.* have synthesized a dendritic unimolecular micelle containing hydrophobic interior and hydrophilic surface functionality to overcome this problem. Unlike polymeric micelles, these unimolecular micelles do not dissociate as they are covalently bound. The internal hydrophobic cavities of this unimolecular micelle were shown to solubilize various hydrophobic guest molecules. Newkome's group has also prepared a series of dendritic molecules possessing internal heterocyclic loci (Newkome *et al*, 1991) capable of specific binding of guest molecules and dendrimers with terminal tryptophan units (Wolinsky *et al*,2008). This provides a basis for dendrimers as drug carriers.

3.1. Dendritic polymers for drug delivery

Polymer based drug delivery systems are designed to improve the pharmacokinetics and biodistribution of a drug and/or provide controlled release kinetics to the specific target. Ideal dendritic polymers should exhibit high aqueous solubility and drug loading capacity, biodegradability and low toxicity. In dendritic polymers drug delivery, a drug is either encapsulated in the interior of the polymer and/or it can be conjugated at the surface terminal to form macromolecular prodrugs.

3.2. Drug encapsulated dendritic polymer

Poly(glycerol succinic acid) dendrimers (PGLSA dendrimers) were investigated as a container for camptothecin, a group of naturally derived hydrophobic compounds with anti cancer activity. The anti cancer activity was investigated for human cancer cells such as HT 29 colon cancer, MCF-7 breast carcinoma, NCI-H460 large lung carcinoma and SF-268 astrocytoma ((Wolinsky *et al*,2008).).

To improve the solubility of the dendrimers, carboxylate (G4-PGLSA-COONa) at the pheripheral groups were used and succesfully encapsulated with 10 hydroxycamptotecin (10 HCPT) (**Fig. 8**). Upon exposure to MCF-7 human breast cancer cells, the unloaded dendrimer showed no cytotoxicity while 10 HCPT encapsulated with G4-PGLSA-COONa showed significant toxicity with less than 5% of viable cells at higher concentrations (20 μM) (Wolinsky *et al*,2008).

3.3. Drug conjugated dendritic polymer

Dendritic drug conjugates or prodrugs consist of a drug that is chemically bound to the peripheral groups of macromolecules. There are three pathways to create these prodrugs; i) direct conjugation of the drugs to the dendritic surface, ii) conjugation via a linker molecule and iii) drug molecules can become an integral part of the dendritic carrier and released through certain triggering events at the desired location. PAMAM-G2.5-COOH (**Fig. 9**) and PAMAM-G3-NH_2 has been conjugated with the methotrexate drug (Gudag *et al*, 2006).

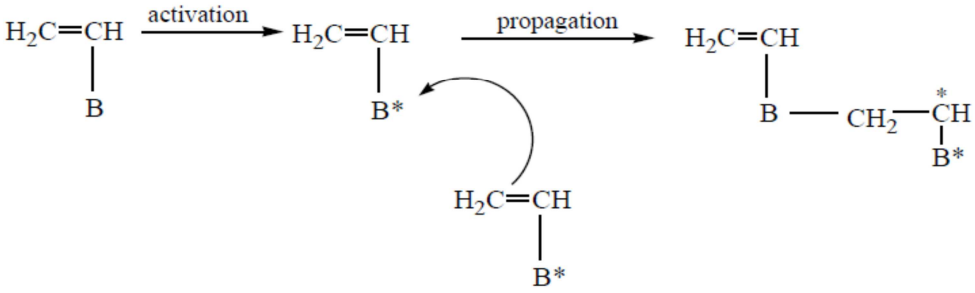

Fig. 6: Self-condensing vinyl polymerisation

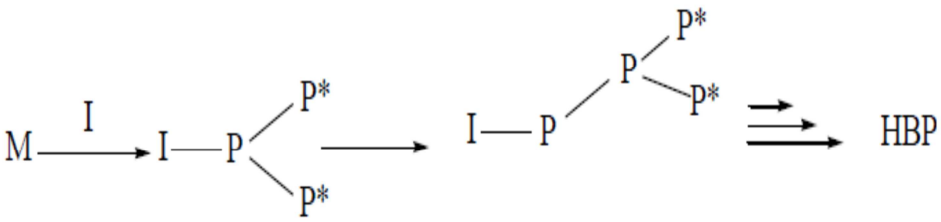

Fig.7: **Ring-opening polymerisation**

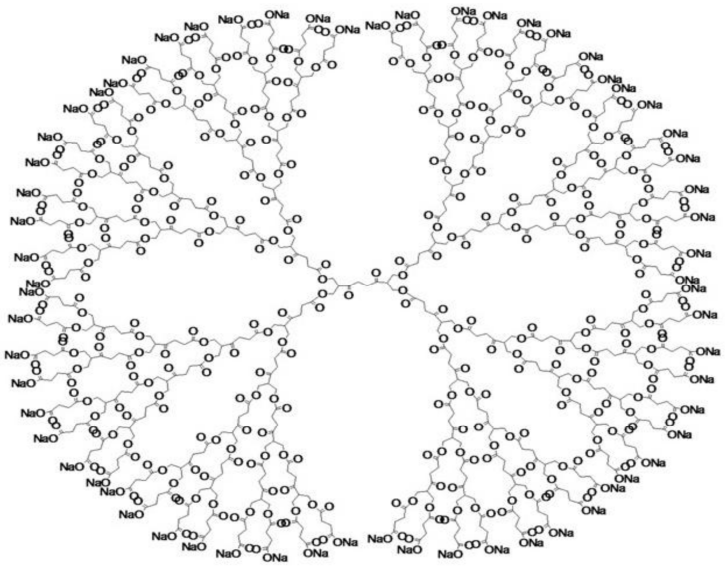

Fig. 8: **Encapsulated G4-PGLSA-COONa dendrimers with 10 Hydroxycamptothecin[33]**

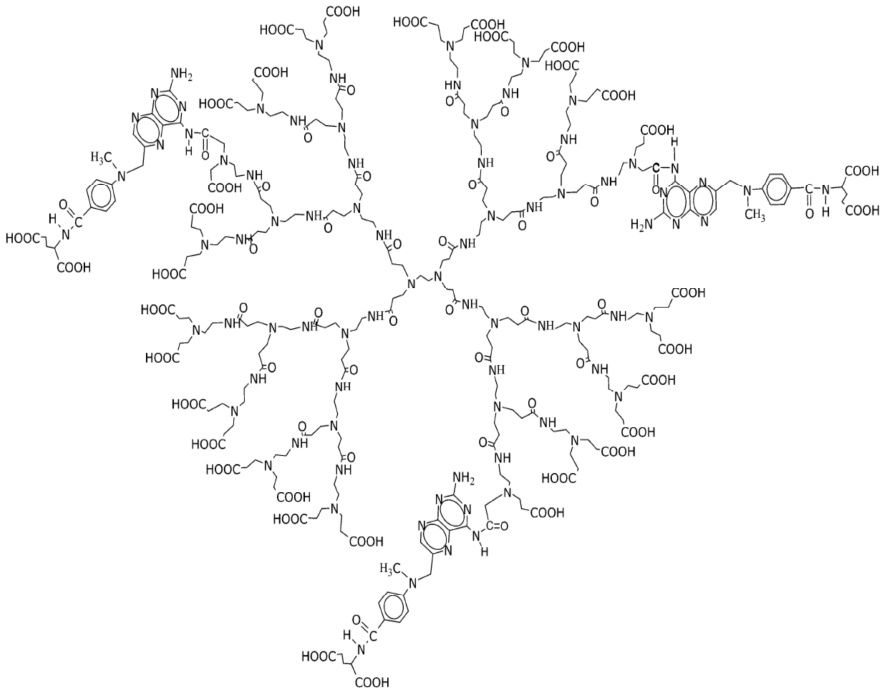

Fig.9: PAMAM-G2.5-COOH conjugated with methotrexate drug

3.4. Dendrimers and Common Drug Delivery Pathways

3.4. 1. Oral Drug Delivery

Amongst the many routes for drug delivery, the oral route is preferred (Gula *et al*, 2013)(Ahn *et al*, 2013)(Sangwai *et al*, 2013)(Higuchi *et al*, 1983)(Mitra *et al* ,1983), probably because of patience preference. For many existing and new drugs such as therapeutic peptides, peptidomimetics, oligonucleotides and others, oral bioavailability is in many cases below acceptablelevels. To overcome this problem and to guarantee a sufficient high oral uptake, the use of efficientoral drug delivery systems is important. Transport of a dendrimer through the epithelial layer of the gastrointestinal tract depends upon the dendrimer's characteristics. Housing a drug inside a soluble dendrimer host not only solubilizes it but also allows it to bypass using a transporter protein for movement from the intestinal tract into the blood. Often drugs are not compatible with use of the protein transporter system that is designed to pass nutrients. The oral route using dendrimers looks very promising especially with anticancer and antihypertensive drugs (Sadekar *et al*,2013)(Kulhari *et al*, 2013)(Gajbhiye *et al*,2008)(Ke *et al*, 2008) (Kolhatkar *et al*, 2008).

3.4. 2. Transdermal Drug Delivery

The human skin is a readily accessible surface for drug delivery. Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms. It is also of great advantage in patients who are nauseated or unconscious. Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on internal organs such as the stomach and intestine. In addition, drugs that are degraded by the enzymes and acids in the gastrointestinal system may also be good targets. However, many new drugs are hydrophobic causing low water-solubility that results in insufficient levels of drug delivered into cells. Water soluble and biocompatible dendritic species are known to improve drug solubility and plasma circulation time via transdermal formulations and to deliver drugs quickly and effectively (Kalhapure *et al*,2013)(Filipowicz *et al*, 2011)(Borowska *et al*,2010)(Venuganti *et al*,2009)(Cheng *et al*, 2007) (Chauhan *et al*, 2003). In this regard, dendrimers have been shown to be useful as transdermal drug delivery systems for various types of medications [46, 49, 50], including anticancer, antiviral, nonsteroidal anti-inflammatory and antihypertensive drugs.

3.4. 3. Ocular Drug Delivery

Ocular drug delivery has been a major challenge to pharmacologists and drug delivery researchers due to the eye's unique anatomy and physiology (Gaudana et al, 2010). The most common route of administration for the treatment of various ocular diseases is the topical application of drugs to the eye. Because of drainage of the excess fluid via the nasolacrimal duct and elimination by tear turnover, the intraocular bioavailability of topically administered drugs is poor. Research

advances have shown that the use of drug delivery systems such dendrimers can help to overcome the many disadvantages and complications associated with ocular drug delivery (Yang et al,2006)(Kambhampati et al,2013).

3.4. 4. Drug Delivery by Injection

Drug administration by injection encompasses intramuscular (IM), intravenous (IV), and subcutaneous (SC) drug administrations. Medication delivered via injection often acts rapidly and has essentially high bioavailability. Injections are useful for drugs that are poorly absorbed or ineffective when given orally. Injection is also an excellent way to administer drugs to patients who are nauseated or unconscious. However, because the drug is delivered to the site of action extremely rapidly with IV injection, there is a risk of overdose if the dose has been calculated incorrectly, and there is an increased risk of side effects if the drug is administered too rapidly. Numerous reports of IV administered dendrimer-drug complexes have appeared (Fernandez *et al,* 2008) (Kaminskas *et al,* 2009) (Merkel *et al,*2010)(Navath *et al,*2008)(Ward *et al,*2013). For example, 2'-(benzo[1,2-c] 1,2,5- oxadiazol-5(6)-yl(N1-oxide) methylidene)-1-methoxy methane hydrazide presents antichagasic activity but has low water solubility. Guest–host interactions with a dendrimer result in good drug solubilization. These interactions can be controlled by varying the solution pH, allowing drug deliverance .

3.4. Covalent and Non-Covalent Dendrimer-Drug Systems

Polymer therapeutics includes polymeric drugs, polymer-drug conjugates, polymer-protein conjugates, polymer-DNA complexes, and polymeric micelles to which drugs are covalently linked and/or physically entrapped (Duncan *et al,*2006)(Harris, *et al,*2003)(Bae *et al,*2003)(Kataoka *et al,* 2001)(Kataoka *et al,* 2001)(Vasey *et al* , 1999). Conventionally, nanoscale therapeutics is derived from polymer-drug conjugates, in which a drug is covalently bound through cleavable linkages such as the pH sensitive *cis*-aconityl, hydrazine, and acetal linkages (Gillies *et al,*2005)(Gillies *et al,*2004)(Vander *et al* 2010). On the other hand, supramolecular drug delivery systems based on block copolymer micelles or dendritic systems have shown great promise and utility for tumor targeting and drug delivery (Nakanishi *et al,*2001)(Haag *et al,*2004). Both covalent and non-covalent systems can utilize the enhanced permeability and retention (EPR) phenomenon (Maeda *et al,*2000)(Seymour *et al,*1992)(Duncan *et al,*1998). Major disadvantages of drug delivery systems based on non-covalent entrapment of drugs into core-shell architectures are the lack of kinetic stability of polymer micelles that are susceptible to infinite dilution arising from their administration and poor drug loading capacity. Nevertheless, reports of simple yet effective and versatile approaches that employ non-covalent interactions for mediating the formation of macromolecular assemblies to encapsulate, transport, and release therapeutic agents have appeared (Kim *et al,*2009)(Skey *et al,* 2010)(Moughton *et al,*2008)(Fukushima *et al,*2008)(Nederberg *et al,* 2009).

To achieve positive results in the encapsulation and release of a guest drug, suitable dendrimer-guest partners must be carefully selected. For example, the complexation of opposite charged PEG block copolymers with cationic amino methacrylates or anionic styrene sulfonates has been explored (Weaver *et al* 2004). Polymer-drug partners with specific acid-base interactions between hydrophobic drug molecules (R1–COOH) and polymer segments (NH2–R2) improved the drug loading capacity (Giacomelli *et al,* 2007). Hydrogen bonding formation between the guest drug and the host polymer has also been explored (Chiang *et al,* 2013)(Hutin *et al,*2013)(Zhu *et al,*2013)(adi *et al,*2013)(Sanyakamdhorn *et al,*2013)(Kim *et al,*2010). Another innovative way to deliver a drug conjugated to or adhering to a dendrimer is to further conjugate the dendrimer to aptamers (Zhou *et al,*2009) (Battig *et al,*2012)(Zhang *et al,*2012)(Soontornworajit *et al,*2010)(Zhou *et al,*2010). The aptamers can be selected to bind to specific cell types, such as cancer or other disease cells with different cell-surface biomarkers. For example, carboxy-coated PAMAM dendrimers were conjugated to amino groups of the aptamers by forming activated esters from the carboxy groups . Such an approach could easily be adapted to carboxy-coated polyester dendrimers that would have the advantage of having low toxicity and biocompatibility associated with polyester dendrimers.

4. Conclusion

The dendritic polymer includes both dendrimers and hyper branched polymer**.** Dendrimers are synthetic, highly branched, spherical, mono-disperse macromolecules of nanometer dimensions, prepared by the iterative synthetic methodology. Although dendrimer drug-delivery is in its infancy, it offers several attractive features. It provides a uniform platform for drug attachment that has the ability to bind and release drugs through several mechanisms. Although toxicity problems may exist, modification of the

structure should resolve these issues. Further work is needed to define the structure of the polymer and the relationship between the polymer and drug molecules for this technology to succeed in drug delivery.

"Cite this Article"

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