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A comprehensive review on dendrimers drug delivery system

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Abstract
Dendrimers chemistry is one of the most rapidly expanding area of modern chemistry. Dendrimers are nano-sized radially symmetric molecule with well-defined homogeneous and monodisperse structure that has a typically symmetric core an inner shell an outer shell. Dendrimers are a promising drug tool, widely, been explored for the treatment, diagnosis or theragnostic purpose. A variety of dendrimers exist, and each has biological properties such as polyvalency, self- assembling, electrostatic, interactions, chemical stability, low toxicity and solubility. Dendrimers has highly compact and tree-like branched structure as well as the uniform size in the nanometer size range have attracted tremendous scientific interest in many fields such as nano-material, biochemistry, supermolecule, drug delivery system etc.

Keywords: dendrimer, types, synthesis, application

Introduction
The word dendrimer is originated from Greek word "Dendron" means "Tree or Branches" and "Meros" means "Parts" i.e., Tree liked branched structure was obtained [1]. In year 1978 dendrimer has been proposed by Sir Vogtle and co-worker, it was the first time that overall complete synthesis of dendrimer was obtained [2]. This was followed by independent development of the divergent macromolecule synthesis of dendrimer by Tomalia in year 1984-1985. It also first time that PAMAM dendrimer were obtained completely. Then in year 1990 convergent synthesis method was proposed by Frechet [3]. Dendrimer in drug delivery system has attracted more attention in recent years [4, 5]. Dendrimer is made of polymer contain empty inner cavity, which is being used for drug encapsulation o hydrophobic drug molecule. The outermost shell is responsible for the reactivity and thus dendrimer is modified or conjugated by a guest molecule. Due to these specific properties of dendrimer, it is suitable for drug delivery system. Dendrimer are new generation highly branch polymer with radially symmetric molecules, Nano-size widely used in drug delivery system. Dendrimer are three-dimensional, monodisperse, globular macromolecules having high number of functional groups on functional group on surface [6, 7]. Due to high surface functional of highly branch polymeric dendrimer enhances the solubility, stability, higher density, lesser viscosity of many drugs [8]. Dendrimer based drug delivery system, gene delivery, solubility enhancer, transdermal drug delivery nanomaterial are some applications of dendrimer [9].

Structure of Dendrimer
The structure of dendrimer consists of three different components they are

1. Central core
The central core should contain relative functional group

2. Repeated branches
The repeated branch should organize in series of generation

3. Surface functional groups
The surface functional group should determine physical properties and location of molecules [10].

Dendrimer is a polymeric molecule composed of multi branched monomers that radially form a central a central core, and obtain like a branch tree. Because dendrimer word is derived from Greek word “Dendron” means “Tree or Branches” and “Meros” means “Parts”. As central core is separated from dendrimer molecule a number identical fragments called “Dendron” are obtained [5]. The number of dendron obtained depends upon central core (2, 3, 4, and more). Dendrimer with high generation such as G-4, G-5 are large, branched with more end groups, while the low generation such as G-1, G-2, G-3 are short and less branched from core to its end as compared to high generation dendrimers [11, 12]. Dendrimer having multivalency is the most advantageous property. Dendrimer increasing in weight and generation of molecules results in closely pack of terminal unit, i.e., its end group are closely packed [13]. Dendrimers solubility also depends upon its end group whether they are hydrophobic or hydrophilic terminal unit, because hydrophobic are soluble in non-polar solvent (non-water, benzene, chloroform) while hydrophilic are soluble in polar solvent (water) [14].

The presence of core shell in dendrimer are used for encapsulation of chemical, API, drugs for their functionality, Drug molecule such as doxorubicin, methotrexate, indomethacin etc. [15, 16].

Synthesis of Dendrimers

Dendrimers are synthesis by four different methods [17, 18]

1. Divergent method
2. Convergent method
3. Hypercores and branched monomer
4. Double exponential and mixed growth

Divergent method

In year 1984 Poly (amino amine) i.e., PAMAM dendrimer was synthesis and published with the help of divergent method [19]. Divergent method starts from the central core and extended toward the surface; the central core contains relative functional group. Divergent method is multifunctional and step wise synthesis. In initial step core molecule like EDA ethylene diamine is take and with help of Michael addition reaction four arms of nitrogen are attached to EDA. In second step EDA is again reacted with amination reaction, this step may repeat multiple time to obtained differential generation of dendrimer. Each step of the divergent method should be completed to avoid mistake in generation, because if some branches remain shorter as compare to other branches may causes impurities, functionality, symmetry of dendrimer [20]. The size different between perfect and imperfect is very small due to which it is difficult to separate. This is the major disadvantages of dendrimers method. To reduce or remove imperfection and side reaction it is necessary to use a large excess of reagents.

Convergent method

Convergent method of dendrimer synthesis was introduced by Frechet in year 1990. This method overcome the purity and structural defects issues of divergent synthesis. By convergent method symmetric and uniform dendrimer are synthesis but the overall yield is less. The yield is reduced for the uniformity of the purity as well as it is laboratory scale dendrimer synthesis. For large scale mostly divergent method is preferred [21].

In convergent synthesis method the dendron end up to terminal group are synthesis initially and in final step it links with core material, for complete structure formation, Due to the steric hindrance between dendron and core the size obtained in convergent method is limited. This limitation is not observed in dendrimer synthesis [22, 23].

Hypercores and branched monomer

To overcome all the errors occurring in divergent and convergent method, Hypercores and branched monomer where introduced [24]. In Hypercores and branched monomer there is involment of pre- assembly of oligomeric species which may linked together to give dendrimer in few steps or higher yield branch upon branch. In this method the core is reacted with one or more molecules of reagent containing at least protection branching site [25].

Double exponential and mixed growth

Double exponential and mixed growth are similar in the method preparation of monomers, the preparation is done by both divergent and convergent method growth from a single starting material [26]. These is also similar to rapid growth technique for linear polymer. The resulting product are reacted to give an orthogonally protected frame which can used to grow again and again by generation to generation. The major advantage of double exponential mixed growth is rapid synthesis [18].

Types of Dendrimers

1. PAMAM Dendrimer

Ploy (amidoamine) dendrimer i.e., PAMAM dendrimer are synthesis by divergent method by Fritz and Vogtle in 1978. The synthesis of divergent method starts from ammino or ethylenediamine core reagent and gives product up to 10- generations. PAMAM dendrimer were also synthesis successfully by Tomalin in 1983 and in 1985, by George R. Newkome in year 1985, Denkewalter at Allied Corporation in 1981 [27].

PAMAM dendrimer has great biocompatibility than other dendrimer families due to combination of interior amino bond and surface amine. PAMAM dendrimer contain positive charge on the surface due to which it has ability for condensation [28].

2. PPI Dendrimer

Poly (propylene imine) dendrimer i.e., PPI dendrimer also called as Astramol dendrimer, DAB-Am-X dendrimer, here DAB stand for diaminobutane core or 1,4- diaminobutane and used as dendrimer core. PPI dendrimer contain nitrogen of primary amine and nitrogen of tertiary amine [22]. The PPI dendrimer are synthesis by divergent method in step wise process (a) the sequence of double Michael addition of acrylonitrile to primary amine followed by (b) catalyzed hydrogenation of nitrile which repeated the reaction result in doubling of number of primary amines [29].

3. Tecto Dendrimer

Tecto dendrimer also called as core-shell dendrimer because tecto dendrimer are composed of a core dendrimer [30], which may contain therapeutic agent or may not contain therapeutic agent and are surrounded by dendrimer

each one of those perform a specific function leading to a smart therapeutic system [31]. Tecto dendrimer fix the target site and deliver API to the recognized diseases cell. Different component of tecto dendrimer perform different function ranging from diseased cell, recognition, diagnosis of diseases, drug delivery, therapy [32].

4. Peptide Dendrimer

Peptide dendrimer are synthesizing through polymerization of amino acid or small peptide unit. Scientifically peptide dendrimer is classified in three categories such as; Type1, Type2, Type3 where type1 and type2 are covalent peptide dendrimer prepared by synthesis of natural amino acid [33]. While type3 is non-covalent peptide dendrimer commercially available core for the syntheses of peptide dendrimer is PAMAM dendrimer core synthesizes by divergent or convergent method PAMAM core attached to protein or peptide result in various function peptide dendrimer. Peptide dendrimer have been used in industry as surfactant. In biomedical peptide dendrimer are used as multiple antigen peptide also used as catalytic and gene and drug delivery vehicles [34, 35].

5. Frechet Type Dendrimer

Frechet type dendrimer was synthesis by hawker and Frechet. Frechet type dendrimer contain poly-benzyl ether as hyperbranched skeleton with carboxylic group as terminal group [1, 36].

Application of Dendrimer in different route of administration

Dendrimer has been evaluated for different route of drug administration system, generally dendrimer is made up polymer, contains macromolecule, core-shell where there is a void place in which drug molecule can easily fix or get encapsulated. Due to which drug release at the targeted site or in a suitable environment. Dendrimer in different route of administration in ocular drug delivery system, transdermal drug delivery system, oral drug delivery system, pulmonary drug delivery system [37].

1. Dendrimer in Ocular Drug Delivery System

In dendrimer ocular drug delivery system topical application of active drugs to the eye is most sensitive and approved route of administration, for the cure of various ocular disorder [38]. Dendrimer in ocular drug delivery convert complex solution to unique solution and overcome on many drugs delivery problem such as irritation, redness, swelling etc., An accurate ocular drug delivery product should be non-irritating, sterile, isotonic, biodegradable, biocompatible. In ocular drug delivery administrated drug reaches to the retina choroidal tissue via blood circulation, where minimum amount of administered drug can get across the cornea, sclera to injured site, because of barrier between blood and eye tissue, hence maximum (e.g.,2-4 drops) amount of drug is administered frequently [39].

Dendrimer with distinct property form a polymer this traditional polymer is suggested as ophthalmic vehicle in ocular delivery system. The advantageous of polymer is it dissolve hydrophobic drug in its cavities and accomplish controlled release and sustain release. Vandamme and Broket in 2004 to 2005 has reported development of ophthalmic vehicle in ocular drug delivery by using PAMAM dendrimer. PAMAM dendrimer with hydroxyl or carboxylic surface group improve bioavailability and residence time of pilocarpine in the eye [40].

2. Dendrimer in Transdermal Drug Delivery System

Drug delivery through skin to attain systemic effect of rug known as transdermal drug delivery [41]. Dendrimer in transdermal drug delivery improve drug proportion such as plasma circulation time, solubility, due to its water-soluble properties and biocompatibility. Dendrimer has investigated for transdermal drug delivery system because (a) presence of hydrophobic moieties result as poor water solubility which restricts the entry of drug in biological compartment. (b) high water solubility and biocompatibility of most of the pre- meditated dendrimer [42]. Dendrimer has been used with NSAIDs for transdermal drug delivery. The uses of NSAIDs are limited due to cause of adverse reaction such as GI, renal side effect. This drawback can overcome by using PAMAM dendrimer complex with NSAIDs like ketoprofen, which enhance penetration and bioavailability of PAMAN dendrimer by using indomethacin as the model drug in transdermal drug delivery application. Cheng and coworker develop the conjugation of ketoprofen and diflunisal with 5.0G PAMAM dendrimer [43].

3. Dendrimer in Oral Drug Delivery

Oral drug delivery system is the most convenient administration route with great patient compliance. Oral drug delivery may display toxicity, low penetration across intestinal membrane [44]. Dendrimer in oral drug delivery system overcomes on those drawbacks. Several systems were used for drug loading in to oral drug carrier [45]. Absorption, Distribution, Solubility in mainly depend on macromolecule carriers, macromolecular are the carriers in which drug is loaded, the main purpose of macromolecule is to minimize the side effect by modifying its structure [46, 47].

Macromolecular carrier of oral drug delivery should protect drug from degradation, carrier reduce nonspecific interaction with food protein and enhance absorption across the intestinal epithelium. Dendrimer may increase the solubility, stability, of orally administered drug in biological environment [48]. Dendrimer easily penetrate through intestinal membrane and enhance the oral observation of low penetration drug due to these unique properties dendrimer is suitable carrier for the development of oral drug delivery system [49].

Duncan and coworker reported the effect of dendrimer size, charge and concentration on uptake by the adult rat intestine and studied the absorption mechanism of dendrimer in intestinal tissue to develop PAMAM dendrimer as potential oral drug carrier [50]. In this study size was the key factor therefore G-2.5 to G-3.5 PAMAM dendrimer transport across the intestinal tissue whereas G-4 high generation PAMAM dendrimer attach to plasma membrane and enter cells by specific absorptive endocytosis [51].

4. Dendrimer in pulmonary delivery

Pulmonary drug delivery system is the alternative to oral drug delivery system pulmonary delivery is for treatment for respiratory diseases the drug is absorbed in alveolar region, lungs. PAMAM dendrimer has been studied for pulmonary drug delivery by measuring plasma anti-factor Xa activity [52]. The study found that the PAMAM dendrimer enhance the pulmonary absorption of enoxaparin, enoxaparin is an anticoagulant and used for prevention of harmful blood clots [53]. It was experimented that G-3, G-2 generation increases or decreases the PAMAM dendrimer activities. It was found that G-3 generation PAMAM dendrimer increases the relative bioavailability of Enoxaparin by 40% to 50%, while G-2, G-2.5 PAMAM dendrimer contain negatively charged carboxylic group which has no effect. As a result, positively charged dendrimer are appropriate carrier for enoxaparin dendrimer in Pulmonary drug delivery [54].

5. Dendrimer as solubility enhancer

Dendrimer molecule include hydrophilic exterior and hydrophilic interior and form covalent complex as well as non- covalent complex, which are responsible for its unimolecular micelle nature [55]. PAMAM dendrimer has potential to enhance solubility in drug delivery system [56]. Dendrimer has unimolecular micelle nature due to which it does not possess a critical micelle concentration, due to this property poorly soluble drug are made soluble by encapsulating them within dendrimer structure. Dendrimer based nanocarrier enhance the oral bioavailability in oral drug delivery system [57].

6. Dendrimer as Gene Delivery

Dendrimer as gene Delivery is the process in which DNA is attached to nanoparticle of inert solid, which is targeted to cell molecules [58]. Dendrimer has the potential to deliver DNA fragments to required parts of cell including many challenges. Dendrimer as gen delivery was primarily reported by the group of Szoka and Baker. Dendrimer as gene delivery use vector as a carrier vector may be viral or non-viral. The purpose of vector is to transfer gene through the cell membrane into nucleus. The polyatomic compound are used as non-viral gene transfer [59]. The compound are PEI, polylysine, and cationic. Dendrimer has the non-immunogenic properties due to this property it acts as a good carrier structure for drugs or bioactive molecule within biodegradable polymer films [60].

Conclusion

Present review present various types of dendrimers, synthesis of dendrimer, and application of dendrimer in pharmaceutical and non- pharmaceutical field. Dendrimer has expanded its approaches in pharmaceutical field and diagnostic field in recent years. As dendrimer possess unique properties such as high surface functional, highly branch polymer, multivalency, globular structure and well-defined molecule weight for drug delivery. Due to those properties, it is the platform for drug attachment and has the ability to encapsulate or bind drug. This review provides complete information about drug carrier, polymer, molecule etc., Many drug has problem of poorly soluble, bioavailability and permeability, Dendrimer drug delivery overcome on those drawbacks. According to, above conclude that more research is needed on the safety, in-vivo stability of dendrimer as to make it substitute for polymer in the future.

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