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Dendrimers as potential platform in nanotechnology-based drug delivery systems

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Abstract*—The dendrimers of poly (amidoamine) (PAMAM) are nanoparticles which have proven succeed in transporting drugs due to high solubility, low toxicity and ability to control drugs release. Studies have explored the biological potential of dendrimers such as to transport genes, development of vaccines, antiviral, antibacterial and anticancer therapies. This review of literature on the PAMAM dendrimers discusses the architecture and general construction of dendrimers and intrinsic properties of the PAMAM. This study also describes how the PAMAM interact with many drugs and the potential of these macromolecules as well as drug nanocarriers in transdermal routes of administration, ocular, respiratory, oral and intravenous administration. Dendrimers promises good future prospects for the biomedicine.

***Keywords*—Dendrimers, Nanocarriers , PAMAM Poly (amidoamine), Pharmaceutical application**

I. INTRODUCTION

About 40% of all drugs developed by the pharmaceutical industry are rejected because they are unable to obtain real therapeutic benefits as a result of the low permeability of cell membranes or very poor solubility in water, reducing bioavailability [1]. Side effects from drugs therapy are consequences of administration of conventional drugs that when reaching the target, eventually reaching other body sites not related to the disease. However, with advances in nanotechnology and other drug problems make these solutions the era of nanotechnology drugs, since they are produced with a special structure for releasing the drug in its target site to confer selectivity [2]. Furthermore, the nanoparticles smart facilitate passage through biological barriers, potential obstacles for the free drug [3]. Among the latest generations of nanosystems are dendrimers that constitute potential drug carriers [4]. These highly symmetrical and branched polymers have attracted much attention in recent years due to their specific physical and chemical properties arising from its organized construction [5]. Among the dendrimers contemporary skilled in the delivery of functional molecules are dendrimers poly (amidoamine) (PAMAM), which have been studied in drug formulations like anti-nflammatory, antimicrobial, antiviral, anticancer [6]. This study is justified by increasing production of scientific research on the PAMAM, since the ability of these polymers to improve the physical and chemical characteristics of the drugs with intrinsic problems. This literature has therefore scoped contribute as a source of knowledge about some of the therapeutic applications of PAMAM. In this literature review the first part will present the dendrimers through the general definition, description of their constituents and structural synthesis methods. While in the second step occurs an explanation of the PAMAM specifying about their synthesis, properties, toxicity, pegylation and the types of drugs incorporation in the dendrimer. Lastly, examples are given of how PAMAM can aid in drug administration by various routes.

II. DENDRIMERS GENERAL STRUCTURE

Dendrimers are also known as arboróis, cascade molecules, or highly branched polymers and have been casually discovered by Vogtle and colleagues in 1978 [7]. Dendrimers are polymeric molecules, chemically synthesized with well defined shape, size and nanoscopic physicochemical properties reminiscent of the proteins [8]. These polymers are almost spherical shape tree having diameters generally between 2 and 10 nm [9, 10].

From the chemical point of view, because they are synthetic, the dendrimerscould be from a peptide, lipid, polysaccharide, among other variations [4]. These new structures represent a true revolution in chemistry because of its extremely precise and controlled architecture, giving it a predictable molecular weight, biodegradability and biocompatibility [11].

The dendrimer structure is a further topology found in nature. It may be observed not only in abiotic systems, for example, snow crystals and the shape of lightning but also in the biological world, such as neurons, branches and tree roots in addition to the vascular systems of animals [12, 9]. The dendrimers can be basically divided into three regions: center, branches and surface area [13, 14, 15].

The core determines the shape, size, direction and multiplicity of dendrimers. The middle part is formed by the branching units and functional groups of terminals are macromolecular periphery [16]. Traditionally, the dendrimers are synthesized by branching units, the monomers ABn, which results in a symmetrical with the end groups B [17]. The constituents of dendrimers have ABn $n \geq 2$, but typically $n = 2$ and 3, in other words after each addition of monomers which are arranged in layers around the dendrimer, can be double or triple the number of peripheral groups [18, 19, 20].

Identical monomer units bind repeatedly around a core by means of branch points, sequentially building tree architecture of the polymer [21, 22].The prepared monomers forming layers after each addition in the core, resembling the layers of an onion from the inside to outside arranged in three dimensions. Each of these layers between the concentric core and the periphery is called generation [23, 24].The generation dendritic rises every additional interaction through a sequence of steps consisting of repetitive reactions. Each new synthesized layer becomes a new generation, usually twice as active sites or surface groups and the molecular weight almost doubled compared to the predecessor generation [25, 26]. There may still be a division of the peripheral groups and internal branches of the dendrimer branching into real arms. Such structures are called dendrons and are in large segments branching units radiating from the core functional [27, 28].

The surface of the dendrimer may be formed by passive or reactive terminal groups to perform a variety of functions. Region serving as a polymerization in which each generation is covalently bonded to generate the precursor [29]. The surface groups may function as gates that control the entry and exit of guest molecules from the interior of the dendrimer. These properties also enables better control and biodistribution of the drug by the body [11, 15].

2.1 Synthesis of dendrimers

There are two main schemes of synthesis, which are convergent and divergent strategies for growth [30, 31]. In the divergent approach the growth during synthesis begins at the core in a process that is directed radially to the periphery. The process convergent dendrimer growth begins at the periphery directing the production of synthesis inside [32, 33]. As the two methodologies have advantages and disadvantages, the most appropriate choice will depend mainly on the type of monomer used in the architecture of the polymer target [34]. Unlike the convergent method, the purity and structural uniformity of the products are more difficult to achieve in the divergent approach, since the number of responses that must be completed for each growth stage increases exponential rate, which requires large amounts of reagents. This method is more suitable for production in large scale [32, 35].

The divergent method consists of a growth from the core of the dendrimer where branching is produced by a repetitive series of steps of adding and activation, rapidly multiplying the number of branches [33, 36].The core molecule interacts with the molecule of the monomer having a reactive group and two groups are not reactive, yielding a zero generation dendrimer (G0). Then the new molecular surface is activated for reactions with more monomers [37]. This process can be repeated for several generations [10].The divergent synthesis ends by the addition of functional groups in the branch points the last generation of branches. This iterative process leads to congestion due to the numerous end groups on the dendrimer periphery [38].

The dendrimer is produced by a multifunctional initiator core that reacts with chemically activated focal point (Y) of a branched monomer to synthesize the dendrimers first generation. Higher generation are built by the addition of monomers branched iteratively producing a dendrimer terminated with full chemical functional groups [39].

2.3 PAMAM dendrimer

Poly (amidoamine) (PAMAM) is the most widely studied and characterized, and so the better understood so far. Extensive literature on this polymer focuses on biomedical properties [40, 41].The structure of PAMAM dendrimers starts from a molecule of ammonia (NH_3) or ethylenediamine ($C_2H_8N_2$) as a core which binds to amine groups of branches ($R\text{-}NH_2$) and amide ($\text{-}CONH_2R$) [7, 37].PAMAM dendrimers are biocompatible, water-soluble non-immunogenic and have amine functional groups that are modifiable to enable the connection with guest molecules or target. Through the PAMAM cavities present on its architecture this dendrimer can host various molecules since the presence of amines and amides groups in its skeleton allows such interaction [42]. However, these polymers may have other functional groups in addition to the amine, such as carboxyl and hydroxyl groups, which grows with generations increasing [43]. In addition, each new generation, PAMAM dendrimer doubles the number of functional groups and weight also increases in1 nm diameter of its structure [22, 23].

PAMAM dendrimers are synthesized by divergent method, based on a construction divided into stages in the presence of methanol, around the nucleus chosen, which could be ammonia or ethylenediamine. The two

sequences of steps consisting in (1) alkylation of the amine functional core with methyl acrylate, also known as Michael addition, generating two branches intermediate with ends ester [26]. Following the amidation occurs (2) the esters with ethylene diamine to produce the generation zero (G0) with four terminal amine groups. Similarly, reaction of this intermediate with ethanolamine produces branched (G0) with four OH surface groups [39]. The consecutive repetition of Michael additions with methyl acrylate and ethylenediamine yields amidation with a dendrimer (G1) and higher generations, increasing the size, weight and number of end groups of the dendrimer[42]. The reaction may stop in step addition of methyl acrylate. The methyl ester can undergo hydrolysis, thus generating an intermediate generation dendrimer or half generation (G 0.5), (G 1.5) and so on, with COOH anionic groups [44].

The dendrimers growth becomes gradually thick and its periphery with a closed structure similar to a membrane. This state of critical branching is achieved when the dendrimer, for lack of space, can no longer grow. This phenomenon is called starburst effect, being observed in PAMAM dendrimers after the tenth generation [10, 18, 27].

2.4 Properties of PAMAM dendrimers

2.4.1 Monodispersivity, size and shape

The monodispersion means that the dendrimers has a well defined molecular structure and without large individual variations, in other words, they are homogeneous unlike other polymers due to their controlled synthesis and purification processes. Such control facilitates the research, because it becomes a tool with defined size ranges [45]. The advantage of low polydispersity makes it possible to predict the pharmacokinetic behavior of dendrimers because little variation of molecules weight makes it possible to know the sample movements of these polymers for biological organism [46].

Due to their nanometric scales and other properties that are similar to proteins, dendrimers are also known as artificial proteins and gain attention in studies that make use of their biomimetic properties [40]. The dendrimer can be controlled by molecular engineering so that its size resembling to antibodies, enzymes and globular proteins. The core PAMAM dendrimer generation ammonia 3, 4 and 5 are close in size and shape of insulin (30 Å), cytochrome C (40 Å) and hemoglobin (55 Å), respectively. Because of the similarity with these and other molecules dendrimers can travel efficiently through the body [47].

In the production of PAMAM dendrimers of generation 1 and 10 the diameter of dendrimers with ethylene diamine core grows from 1.1 to 12.4 nm. As this may vary in shape according to the generation, as the generations (G0) to (G3) with ethylenediamine core in ellipsoid shape but the high generation of (G4) to (G10) takes spheroidal form [48]. This is because the dendrimer spreads segments as possible to reduce the repulsion which leads to a globular structure [26].The early generations of the PAMAM dendrimer(G0) and (G1) have highly asymmetric forms and open structures compared with higher generations [49].

2.4.2 Polivalency

The polivalency is related to the quantity of reactive sites on outside of the dendrimer potential to form connections with various materials of interest [50]. Areas of high multivalent dendrimers of generations can contain a large number of functional groups. This makes the surface of the dendrimer branches and more susceptible to interactions with a large number of species [43].

The multivalencyallows better interaction with biological targets since most of the molecular interactions occur through biological multivalent bonds. The valency binder is the number of links that can be established with a receiver or receivers. The strength of multivalent interactions exceeds the sum of the forces [38].

Dendrimers as potential platform in nanotechnology-based drug delivery systems exhibit higher biological activity compared to conventional drug molecules because the dendrimer can react with multiple receivers at once in the biological site of action [51].

2.4.3 Solubility and biocompability

Dendrimers generally have greater solubility in common solvents as compared to linear polymers [30]. However, the solubility depends on various components in addition to the surface groups as the generation number, nature of repeating units and even the core. What enables the construction of dendrimers perfectly soluble in a large number of solvents, ensuring both the solubility of dendrimers in organic solvents, which leads a rapid dissolution in water and enhances the activity of hydrophobic molecules [48]. PAMAM dendrimers have received considerable attention because its ability to solubilize water-insoluble drugs and transporting them through the biomembranes, increasing the bioavailability of these drugs [52, 53].

Before being used as biological agents in drug delivery, dendrimers should meet a variety of requirements such as: (1) having no toxicity, (2) is not immunogenic (3) ability to cross biological barriers such as the walls and the intestinal membranes, (4) remain in circulation long enough to be effective clinically (5) ability to deliver specific structures [54, 55]. The biological properties as, for example, immunogenicity and toxicity depends mainly on the size and the surface groups of the dendrimers. The interior structure therefore

has less influence because usually the dendrimer interactions occur with the outside via the exposed surface groups, which makes the dendrimers able to cross cell surfaces [16].

2.5 Toxicity and pegylation

It is known that the dendrimers may cause toxicity mainly attributed to the interaction of the cationic dendrimers surface with negative biological load membranes damaging cellular membranes causing hemolytic toxicity and cytotoxicity. Therefore, PAMAM dendrimers are more cationic than anionic cytotoxic. An example of interaction with lipid bilayers of cells occurs with the cationic dendrimer-G7 PAMAM which comes to form holes 15-40 nm in diameter, which disturbs the flow of electrolyte causing cell death [24, 56, 44].Many toxic effects of dendrimers are attenuated at their surfaces with hydrophilic molecules and poly (ethylene glycol) (PEG) which masks the surface charge cationic dendrimersimproving biocompatibility and increasing the solubility of the polymers. The pegylateddendrimers have lower cytotoxicity and longer stay in the blood than non-pegylateddendrimers. PEGylation increases the physical dendrimers size which reduces renal clearance since the glomerular filtration limit is reached [1, 57, 58].

2.6 Interactions of drugs with dendrimers

The dendrimers designed for drug delivery have the intention to improve the pharmacokinetics and biodistribution of drugs and may also provide a controlled release of the drug with the goal of reaching the target tissues [59]. Dendrimers interact with drug molecules physically by absorption on surface by electrostatic interactions or by conjugation with the surface groups for covalent bonding or by encapsulation of the drug into the cavities of the dendrimer [60, 61, 62].

The technique of drugs encapsulation may be a purely physical entrapment or involve interactions with specific structures within the dendrimer [63]. The empty internal cavities generally have hydrophobic propertieswhich allow interactions with poorly soluble drugs. The existence of atoms of nitrogen and oxygen in the internal structure of the dendrimer allows interaction by hydrogen bonds with the drug [48].Encapsulation is a general strategy for low molecular weight molecules and are transported on the bioactive surface of dendrimers induce undesired immunogenicity [49].

The high density of functional groups are ionizable at the periphery of the dendrimer (such as amines and carboxyl groups) permits to fix a large number of ionizable drugs by electrostatic interactions and transporting them to their destination [63, 64]. Covalent interaction method offers advantages over previous methods, therefore allow multiple drugs to be attached to each dendrimer through the numerous groups of the surface, the covalent bonds between the drug and the polymer are likely more difficult to break giving them greater control over the drugs, overcoming the force of interaction achieved by electrostatic bonds and encapsulation [34, 59].

2.7 PAMAM applications in drug delivery

Dendrimers can be designed to improve the properties of some drugs in ocular, pulmonary, oral, intravenous,topical and transdermal formulations. TheTable 1 presents the applications of PAMAM dendrimers in various routes.

PAMAM	Drugs	Routes	References
G5-PAMAM	Ketoprofen and	Transdermal	[65]
G4-PAMAM	Indomethacin		[66]
G2-G6-PAMAM	5-fluorouracil	Topic	[67]
G3-PAMAM G5-PAMAM	Nifedipine		[52]
G2-G3-PAMAM	Ketoconazole		[68]
G1.5-4-PAMAM	Pilocarpine nitrate and tropicamide	Ocular	[69]
G3.5-PAMAM	Glucosamine and Glucosamine 6-sulfate		[70]
G3-PAMAM	Brimonidine and timolol maleate		[71]
G2-G3-PAMAM	Enoxaparin	Pulmonary	[72]
G0-G3-PAMAM	Insulin and calcitonin		[73]

G3-PAMAM	Propranolol	Oral	[74]
G5-PAMAM	Ketoprofen		[75]
G0-PAMAM	Naproxen		[76]
G0-G3-PAMAM	Niclosamina		[77]
G3-PAMAM	Sulfamethoxazole		[78]
G0-G3-PAMAM	Furosemide		[79]
G4-PAMAM	Risperidone		[80]
G4-PAMAM	Flurbiprofen	Intravenous	[81]
G4-PAMAM	Indomethacin		[82]
G4-PAMAM	5-fluorouracil		[83]
G3.5-PAMAM	Cisplatin		[84]
G5-PAMAM	Methotrexate		[85]

Source: Adapted from above authors

Dendrimers can be designed to improve the properties of some drugs in topical and transdermal formulations delivering the drug to its destination due to the increased permeation of drug through the skin [86, 87, 88]. Due to its properties, the dendrimers can be used as carriers in the effective ophthalmic drug delivery, since they can suffer from low bioavailability because of the physiological barriers belonging to the eye [89, 90].

The pulmonary route provides a large surface area for delivery of drugs in addition to avoiding first pass metabolism by increasing the systemic bioavailability of the top and become more effective therapeutic action [91]. However, the potential of dendrimers in pulmonary drug delivery still remains as an avenue that needs further research [92]. The oral route is the most popular and acceptable by the patient. Because of this, several studies involving dendrimers have emerged in order to improve the oral absorption of drugs [93, 58].

The intravenous route is not only a simple method also presents itself as the simplest way of delivering a drug to the systemic circulation. However, the low solubility of various drugs has been an important limiting factor for a better use of the intravenous route [94].

III. CONCLUSIONS

PAMAM dendrimers are presented as nanocarriers drugs promising for the coming years, since the multiple properties related to their three-dimensional structure, as mono dispersity, versatility, biocompatibility and other characteristics intrinsic which increase the solubility and activity of these drugs linked these polymers, improving the bioavailability and reduce the toxicity potential of many drugs.The drug can be linked to the dendrimers by covalent bonds, electrostatic interactions, or by encapsulation, and the choice of the interaction fits the drug needs. Furthermore, as a flexible and excellent carrier, the dendrimers can be carefully designed for the delivery of biomolecules to the desired target tissue, which allows the use of lower doses, although effective in therapy. However, dendrimers PAMAM accept various routes of administration, which increases the range of drugs maybe enhanced action in the body which have limited application process options. This versatility can facilitate in the future the safe use of drugs which cannot be used in medicine for reasons of toxicity or low solubility.

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