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PAMAM DENDRIMERS AS DRUG DELIVERY CARRIERS, BENEFITS AGAINST RISKS

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Abstract:

Objectives: *The aim of this review is to provide brief description of synthesis, structure, properties and uses of PAMAM dendrimers with providing some detailed examples of using PAMAM as promising drug delivery carrier.* ***Findings:*** *Dendrimers as novel polymeric symmetric materials with three dimensional architecture represent a growing substrate for drug delivery. They possess different structural and physical properties that enable them to conjugate with different drugs to form organ-targeting drug delivery systems. PAMAM (Polyamidoamine) is the most studied and commercially available type of dendrimers. PAMAM has been reported in different research papers to have many pharmaceutical benefits such as solubility enhancement, permeability enhancement, gene transfer, and organ-targeting drug delivery carrier. PAMAM has some concerns about its cellular toxicity, but many studies suggested its biocompatibility and non-toxicity on biological tissues.* ***Summary:*** *PAMAM dendrimers represent excellent promising drug delivery carrier systems with many benefits and substantial risks which require further studying and challenging*

Key words: *Ciliotoxicity- Dendrimers- PAMAM- Targeted Drug Delivery.*

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INTRODUCTION:

Dendrimers (also known as Dendron, arborols and cascade molecules) were first discovered by Fritz Vögtle in 1978[1].

They are class of novel synthetic polymeric materials that are nanosized, radially symmetrical with well-defined three dimensional spherical architecture and monodisperse structure consisting of tree-like atoms or branches of highly concentrated functional groups with internal diameters generally have ranges between 2 and 10 nm [2-5].

Deeper view of dendrimer structure explores their similarity with natural designes in plants, animals and human, figure (1). Their architecture is similar to tree which extends by its branches over and under the ground to enhance exposure of leaves to sunlight and absorb nutrients and water from the ground. Also dendrimer structure is similar to branched dendritic network of bronchioles and alveoli to give maximum surface for the transfer of oxygen into the blood stream. Dendrimer structure is similar to the structure of Microglia cells in the brain that is when activated during pathological or degenerative states in the brain release its dendritic structure confirming delivery of secreted anti-inflammatory interleukins to the diseased brain tissue [6-7].

Dendrimers are hyperbranched molecules introduced in the time that polymer chemistry and technology traditionally was focusing on linear polymers which are only occasionally contain some smaller or longer branches while recent studies discovered that the properties of highly branched macromolecules can be very different from conventional polymers due to ability of theses terminal functional groups to change the physical and chemical properties of polymer molecule [8-10]. Being polyvalent molecules with high degree of branching, dendrimers have higher aqueous solubility and higher solubility in non polar solutions compared to their analogues of linear polymers with the same molecular mass and the same functional groups [11-12].

In the last years, there was great interest about investigation of using dendrimers for pharmaceutical and biological applications. Their unique architecture and molecular structure enhanced their use in the field of drug delivery as drug carriers and cellular targeting molecules. Many studies investigated their use for topical [13], transdermal [14], nasal [15], ocular [16], pulmonary [17], oral [18] and controlled drug delivery [19].

They are expected to play important role in delivery of anticancer drugs as many studies reported ability and safety of using dendrimers as targeted drug delivery carriers when they are conjugated to the anticancer drugs. This conjugation increases the site-specifity and modifies the biodistribution of the drug which enhances drug bioavailability and reduces its side effects [20-21].

In the field of gene delivery, dendrimers have the ability to transfer genetic material efficiently into the nucleus and cytoplasm of eukaryotic cells which makes them ideal to be used in gene delivery [22-24]. Virus was the first gene delivery success but induction of strong immunogenic response in patients was its limiting step [25].

Dendrimers can represent the macromolecule which is conjugated to small molecules to raise antibodies against it. Also, they have the desired characteristics to act as efficient immune-stimulating compounds (adjuvants) that can increase the efficiency of vaccines [26-27].

Dendrimers are being investigated for some non-pharmaceutical application. For diagnostic purposes, they can be used as contrast agents for magnetic resonance imaging (MRI), functional genomics analysis, and as biosensors for the rapid diagnosis and molecular probes [28].

Depending on their structure, dendrimers are divided into many types, under which there are subtypes. PAMAM [Poly (amido amine)] is the most studied and commercially available type of dendrimers. Other types include MAP-dendrimers (Multiple Antigen Peptide), PPI-dendrimers (Poly-Propylene Imine), POPAM dendrimers (POly -Propylene Amine), PEI-dendrimers (Poly-Ethylene Imine), Tecto Dendrimer, Multilingual Dendrimer, Chiral Dendrimer, Hybrid Dendrimer, Linear Polymer, Micellar Dendrimer, Amphiphilic Dendrimer and Frechet Type Dendrimer [6].

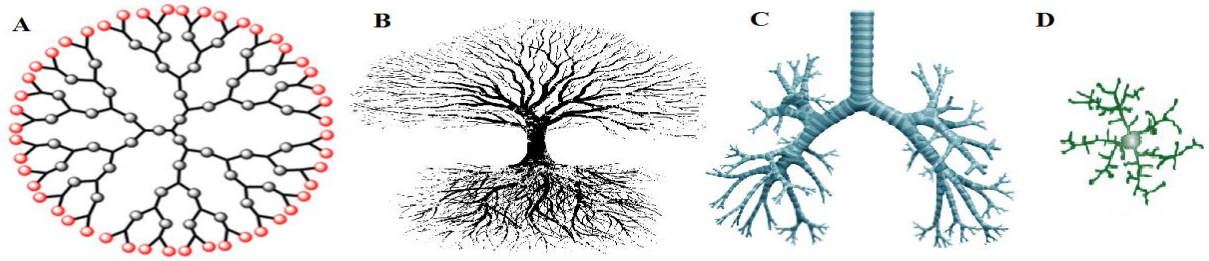

Fig1: Apparent similarity in the architecture of A: Dendrimer, B: Tree, C: Bronchioles and D: Microglia cell

In this review, we will give brief description about dendrimers structure, methods of synthesis and properties, as detailed information are discussed in many other updated reviews. This review will focus on single type of dendrimers, PAMAM dendrimers. We will discuss PAMAM structure, properties, uses, toxicity, and finally we will give detailed examples of using PAMAM as promising drug delivery carriers.

General structure of dendrimers

The architectural structure of dendrimers can be described as follow [29], figure (2).

i) Initiator core (single atom or atomic group)
ii) Interior layers composed of repeating units radically attached to interior core with empty internal cavities (generations)
iii) Exterior (terminal functionality - functional end groups) attached to outermost interior generation.

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 [30].

Dendrimer generation represents the hyper branching when going from the centre of the dendrimer towards the periphery, figure (3), resulting in homo-structural layers between the focal points (branching points) where is identical monomer units bind repeatedly around a core [31], while dendrimer generation number is the number of focal points when going from the core towards the dendrimer surface [32]. That is when the dendrimer has four branching points growing from the centre to the periphery is denoted as the 4th generation. Dendrimer generation plays an important role in the physical and chemical properties of the dendrimer [33]. As the molecule grows bigger, the structure becomes denser and more tightly packed. The shape of lower generation molecules (such as G0, G1, and G2), tend to be asymmetrical, but as the generation number increases, the structure becomes more spherical [34].

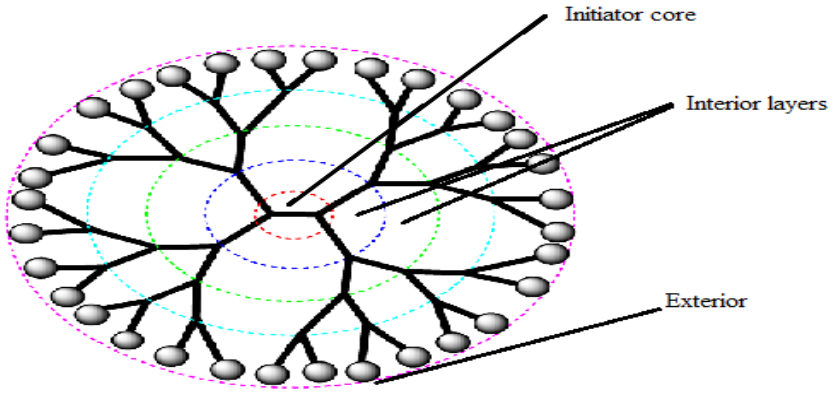

Fig2: The architectural structure of dendrimers

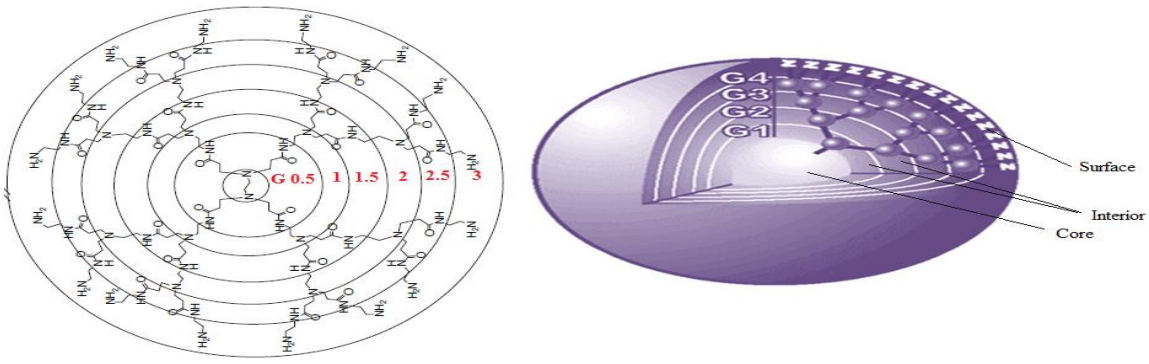

Fig3: Dendrimer generations development

Dendrimers synthesis

Dendrimer are generally prepared using either a divergent method or a convergent one [35-36], while there is a more advanced and recent method called double exponential and mixed method [37-38].

Divergent method, Figure (4)

- The core molecule reacts with monomer molecules or coupling of the monomer occurs.
- Deprotection or transformation of the monomer end-group to create a new reactive surface functionality and then coupling of a new monomer.
- Process repetition for dendrimer growth outwards from the core molecule side reactions and incomplete reactions of the end groups.

Structure defects:

- Large excess of reagents.
- Require extremely efficient reactions in order to ensure low polydispersities
- Difficulties in the purification of the final product.

Convergent method, Figure (5)

- The dendrimer growth starts from the end groups and progresses inwards.
- The large dendrons or branched polymeric arms are attached to a multifunctional core molecule
- Easy to purify the desired product
- Possibility of structure modification through addition of functional groups at the periphery of the macromolecule.

Structure defects:

- Doesn't allow the formation of high generations because steric problems due to reactions of the dendrons and the core molecule.
- Occurrence of defects in the final structure.
- Low yields in the synthesis of large structures.

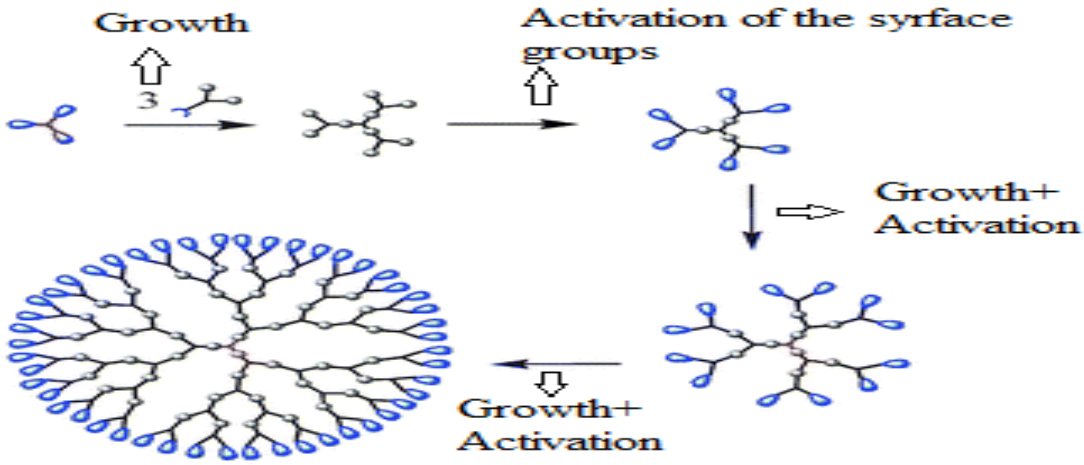

Fig 4: Divergent method of dendrimer synthesis

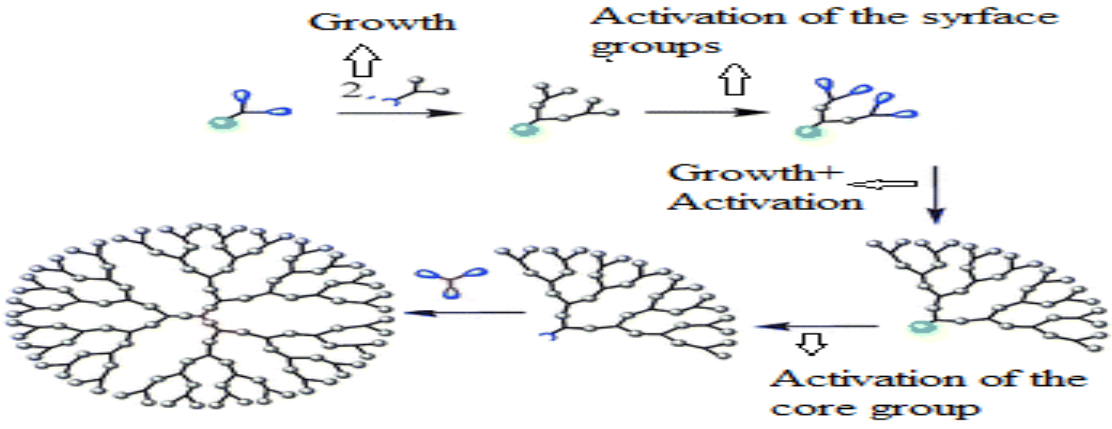

Fig 5: Convergent method of dendrimer synthesis

Double exponential and mixed method, Figure (6)
This method represents a mixture between the two above method. Monomers from single starting materials are prepared by divergent and covalent methods. After that, these two monomers are reacted together to give a trimer which is orthogonally protected and can repeat the growth process again. Strength of double exponential growth is more subtle than the ability to build large dendrimers in relatively few steps. This method allows the combination of divergent and convergent method without their individual structure defects.

Mechanism of dendrimer-drug interaction
Dendrimers can interact with drugs through different mechanisms which can be summarized into three main categories; simple encapsulations, electrostatic interactions and covalent conjugations, figure (7).

Simple encapsulation
Encapsulation is the general strategy for low-molecular weight molecules. Dendrimers which have a hydrophobic interior and hydrophilic chain ends and characterized by ellipsoidal or spheroidal shape, empty internal cavities, and open nature of their architecture can solubilize poorly- soluble drugs in aqueous solutions through host-guest interactions inside their empty cavities (void spaces) [39]. In addition, nitrogen or oxygen atoms in these internal cavities can interact with the drug molecules by hydrogen bond formation.

Eletrostatic interaction
It depends on presence of high density functional groups (such as amine groups and carboxyl groups) on the surface of dendrimers that enable the dendrimer to physically adsorb the drug molecule on the surface through electrostatic interaction which may have potential enhancement of the solubility of the hydrophobic drugs [40].

Covalent conjugation
This mechanism represents covalent attach of one or more than one molecule to the surface groups of the dendrimer which gives this method more advantages then others. It is also characterized by that the covalent bonds between the dendrimer and the drug molecules are difficult to break as it requires chemical or enzymatic cleavage which makes the release of the drug molecules is more controlled [41].

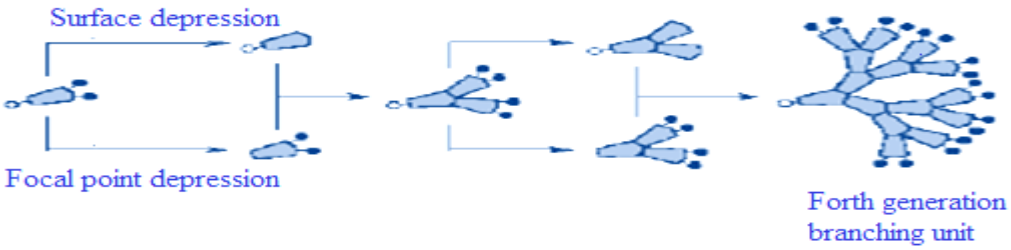

Fig 6: Double exponential method of dendrimer synthesis

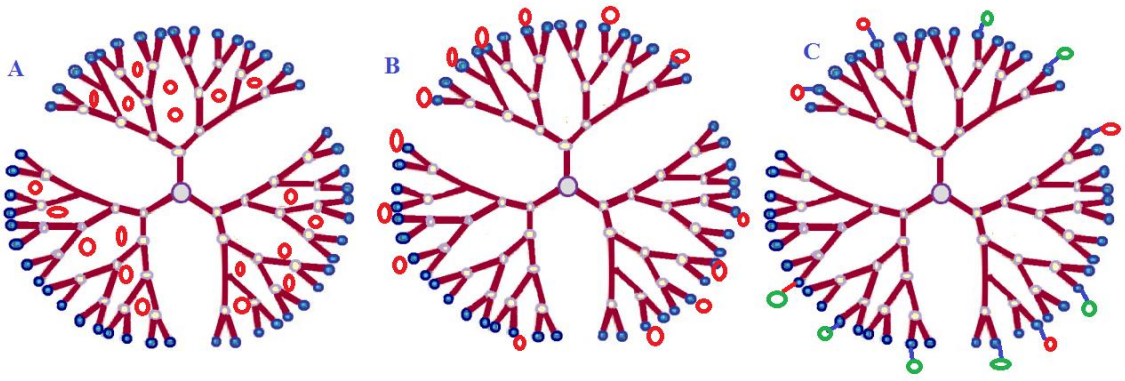

Fig 7: Different dendrimer-drug interaction mechanisms, A: encapsulation method, B: Electrostatic interaction, C: covalent interaction

PAMAM dendrimers

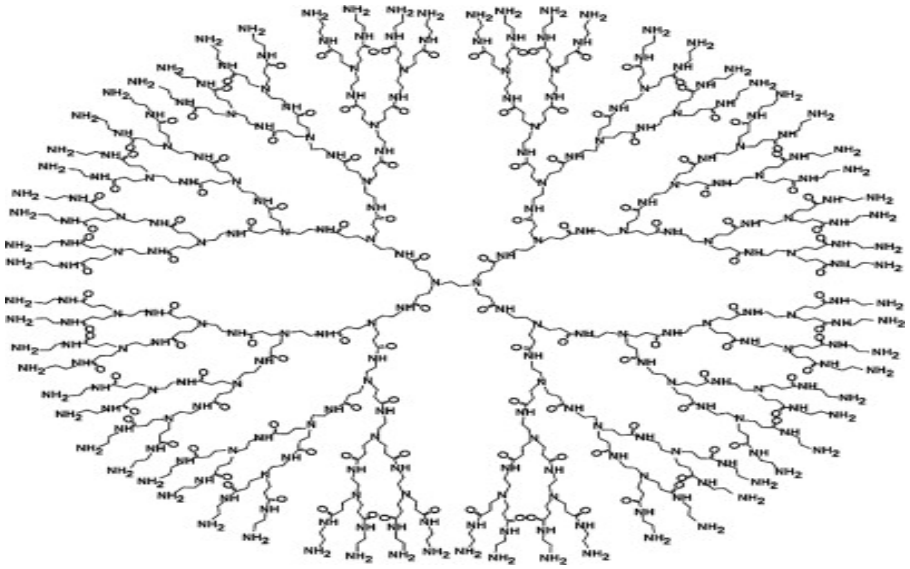

Fig 8: Typical structure of fourth-generation poly(amidoamine) dendrimer [42]

PAMAM dendrimers, figure (8), are the most commercially available dendrimers under the trade name (Starburst™). They are spheroidal or ellipsoidal in shape synthesized by the divergent method with ammonia or ethylenediamine as a starting material. Amine functional groups can be modifiable to enable the connection with guest molecules or target. In addition to amine functional group, they may have carboxyl and hydroxyl groups [43].

They are synthesized in different full generations (G0-G10) and in intermediate generations (G1.5, G2.5, -----etc). Increase the number of generation of PAMAM means increase in the molecular mass and the number of terminal functional groups. That is from one generation to the next one, number of terminal functional groups is doubled as well as the molecular mass with a 1 nm increase in the molecule diameter [44], table (1), figure (9).

Table 1: Molecular mass and number of terminal function groups of different PAMAM generations

Generation	Ammonia core (NH3)		Ethylenediamine core (C2H8N2)	
	molecular mass	number of terminal groups	molecular mass	Number of terminal Groups
0	359	3	516	4
1	1043	6	1428	8
2	2411	12	3252	16
3	5147	24	6900	32
4	10619	48	14196	64
5	21563	96	28788	128
6	43451	192	57972	256
7	87227	384	116340	512
8	174779	768	233076	1024
9	349883	1536	466548	2048
10	700091	3072	933492	4096

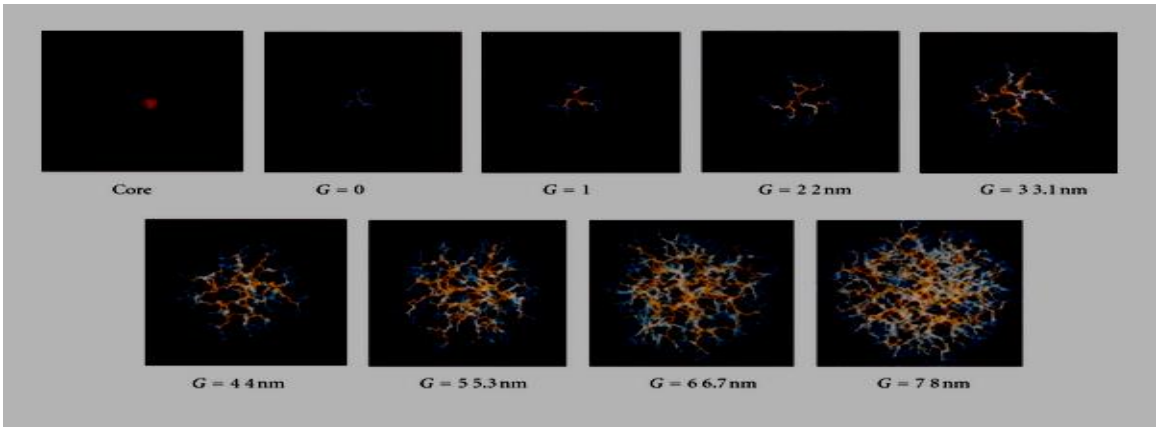

Fig 9: linear increase in diameter and exponential increase in terminal functional groups o different PAMAM generations (G0-G7) [45-46]

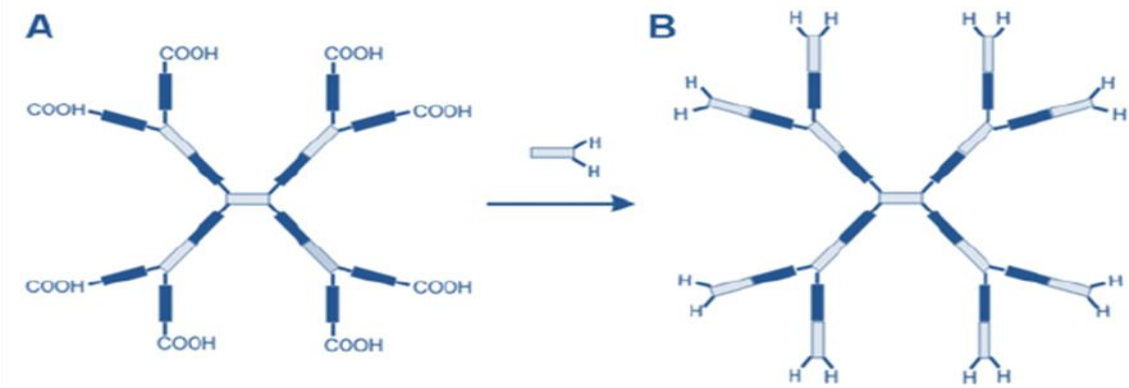

Fig 10: The structure of a half-generation PAMAM dendrimer (A) and a full-generation PAMAM dendrimer (B)

For PAMAMs synthesis using ammonia as a core molecule, they are constructed from both methyl acrylate and ethylenediamine. First, ammonia reacts with methyl acrylate monomers, in presence of methanol, to produce a half generation with anionic carboxyl groups on the surface, then ethylenediamine is added to give a full generation [47-48], figure (10).

Structural and physical properties of PAMAMs

- They are homogeneous and have monodispers architecture with defined molecular structure and low individual variations. This is related to ability to control their method of synthesis and purification.
- They are characterized by the presence of internal cavities and by a large number of reactive end groups.
- They have high solubility and reactivity due to incidence of a number of functional end groups and empty internal cavities PAMAM dendrimers are specially characterized by their ability to solubilize water-insoluble drugs and transporting them through the bio-membranes.
- They are degraded in light [49]. They are usually introduced as methanol solutions in umber glass bottles and all their reactions are mostly done in dark.
- Their extremely precise and controlled architecture gives them a predictable molecular weight, biodegradability and biocompatibility [50-52] which makes them ideal drug nano-carriers and cellular targeting molecules.
- The surface groups may function as gates which control the entry and exit of guest molecules from the interior of the dendrimer. These properties also enable better control and bio-distribution of the drug by the body with predictable drug pharmacokinetics [53-55].
- They, and other dendrimers, are called artificial proteins due to their nano-scale size and biomimetic properties. With the use of molecular engineering, their size can be controlled to

resemble antibodies, enzymes and globular proteins [56].

- Due to the positive charge on their surface, PAMAMs have the ability for condensation of DNA followed by transfection as they form stable complex with DNA that can penetrate cell membrane due to its positive charge to release DNA inside cells. In addition, their surface can be modified to enhance transfection efficiency and specificity to target cells [57-59].

PAMAM toxicity

Despite all the great potential benefits of PAMAMs in the biomedical and pharmaceutical field, their cytotoxic concerns are conflicting. As they are nano-metric molecules (1-100 nm) in size and formulated as drug nano-carriers with low cell-selectivity, they can interact with the nano-metric cellular components of the cell such as enzymes, protein and nucleus [60-62].

PAMAMs are known to have considerable in-vivo and in-vitro toxicity due to the interaction of the cationic surface group (mainly NH2- group) with negative biological membranes, which are negatively charged due to presence of glycolipids and some glycated membrane proteins, leading to cellular membrane damage, hemolysis and lysis [63-64].

They can interact with the lipid bi-layer increasing the permeability and decreasing the biological membrane integrity which may cause disruption of the cell and lysis [65-66].

Therefore, toxicity of cationic dendrimers is controlled by the number of terminal amine function groups on the surface, which increases with increase in dendrimer generation and the dendrimer concentration [67]. High dendrimer generations with neutral and cationic surface groups have higher toxicity than low dendrimer generations with anionic or neutral polar surface groups [66]. So, toxicity of PAMAM dendrimers depends mainly on the pre-dominant charge on the terminal functional groups on the surface in addition to their concentrations. Many studies have explored the toxic effect of PAMAMs.

Bodewein et al, [68] studied the toxic effect of different generations of PAMAMs (G3.0, G3.5, G4.0 and G4.5) in Zebrafish embryo and they found that anionic dendrimers PAMAM (G3.5 and G4.5) have significant lower lethal effect than cationic ones.

Jevprasesphant and his co-workers [69-70] studied the cytotoxicity of PAMAM dendrimers using monolayers of the human colon adenocarcinoma cell line, Caco-2 cells. They reported that cationic PAMAM generations (G2, G3, G4) were toxic while anionic ones (PAMAM G2.5 and PAMAM G3.5) were practically non-toxic.

Jones et al. [71] studied the effect of different PAMAM generations on platlets functions and morphology after intravenous administration in mice. They found that cataionic PAMAM (G7) terminated with amine group activated platelets and dramatically alter their morphology resulting in platelet function alteration including increased aggregation and adherence to surfaces while neutral and anionic PAMAM didn't induce this lethal effect.

In contrary to the above reports, Vandamme and Brobeck [72] reported that the cationic dendrimers (with amine end groups) did not induce more irritation than dendrimers with peripheral carboxylate or neutral functional groups on the ocular tissues.

Fischer et al. [73] have reported that the cytotoxic effect of cationic PAMAM dendrimers on L929 mouse fibroblasts was moderate having high biocompatibility compared to linear polymers.

Approaches to decrease PAMAM toxicity

There are different reported approaches to decrease toxicity associated with PAMAM dendrimers. Surface engineering is important one of these approaches, this strategy depends on the ability of attachment of different moieties with different functional groups to the surface of PAMAMs through covalent or non-covalent bonds. These moieties can protect the cationic amine group from interaction with viable molecules and thus inhibit the toxicity effect [69]. In addition, these moieties with different functional groups can significantly add beneficial properties to the dendrimer such as increase solubility, enhance stability, improve drug bio-distribution and pharmacokinetics, increase drug encapsulation and entrapment, enhance cellular targeting, and modify drug release [74].

PEGylated PAMAMs, with 10% Poly(ethylene glycol), were synthesized by Mustafa, et al. [75] and were characterized in-vitro and in-vivo, PEGylated PAMAMs showed more enhanced solubility, biodistribution and cell transduction over non-PEGylated ones, in addition PEGylated PAMAMs showed no cytotoxicity while non-PEGylated showed significant toxicity when they were tested in Mouse fibroblast cell line L929.

Conjugation with either lauryl chains or polyethylene glycol (PEG) 2000 onto the surface of cationic PAMAM dendrimers results in decreased toxicity due to a reduction and shielding of the positive charge on the dendrimer surface by the attached chains [70]. Other toxicity concerns about PAMAMs will be mentioned under the examples of using PAMAM as drug delivery carriers.

Examples of using PAMAM as drug delivery carriers

5-fluorouracil-PAMAM dendrimer complex [76]

Cervical cancer is a problematic and life-threatening cancer that infects epithelial tissues through micro-abrasions or other epithelial trauma. Studies demonstrated that expression of two high-risk viral oncogenes, E6 and E7, is essential for malignant transformation and maintenance of the malignant phenotype of cervical cancer cells [77].

5-Fluorouracil (5-FU) is widely used to treat cervical cancer through inhibition of the progression of cancer through effective interaction with E6 and E7 oncoproteins [78], but use of 5-Flurouracil has many problems such as the little difference between the minimum effective and maximum tolerated dose, and drug resistance development after prolonged treatment [79-80]. So, providing the drug within an organ-targeting system which releases the drug in a controlled manner is necessary.

In this study, different PAMAM generations (0.5G, 1.0G, 1.5G, 2.0G, and 2.5G) were synthesized and characterized. After studying the cytotoxic effect of the synthesized PAMAMs, it was found that cationic PAMAMs with amine groups on their surface (1.0G and 2.0G) have higher cytotoxic effect than anionic ones with amide and carboxylic groups on the surface (1.5G and 2.5G). This was in accordance with many previous findings [81].

For toxic concerns, only 1.5G and 2.5G PAMAM were conjugated with 5-Flurouracil. The complex formation was emphasized by FTIR, TEM (Transmission electron microscope) and DLS (dynamic light scattering). Both complexes could release the drug in a sustained manner than the free drug following zero order kinetics.

Studying of the effect of the PAMAM-5-Flurouracil complex on cell viability in the HeLa cell line in comparison to the free drug indicated that the complex has more potential killing effect on the cancer cell by inhibiting the E6 and E7oncoproteins than the free drug. On the other side PAMAM- 5-Flurouracile complex has lower side effects than the free drug concerning the amount of WBC (White blood cells), RBC (Red blood cells), and eosinophil. This study proved that utilizing of PAMAM as a carrier for 5-Flurouracil can provide a cancer cell-targeting delivery system with higher effect and lower side effects. Similar results were reported previously by Bhadra et al. [82] who used PEGylated PAMAM dendrimers as a carrier for 5-Flurouracile nanoparticles for cancer treatment.

Capecitabine-PAMAM Dendrimer Complex [83]

Capecitabine is an effective anticancer drug in metastatic breast and colorectal cancer chemotherapy under the trade name Xeloda®. It is enzymatically converted to 5-Flurouracil in the tumor, inhibits DNA synthesis and slows the growth of tumor tissues [84]. Although chemotherapeutic agents have high ability to destroy cancer cells, they are not organ specific and have potential to damage chemotherapeutic agents- sensitive cells such as blood, hair and intestine lining-cells. This damage leads to the commonly induced side effects such as myelosuppression, diarrhea, alopecia, and liver malfunction [85]. So, targeted drug delivery has been the main objective of the cancer treatment.

The capecitabine/PAMAM dendrimer complex was prepared at different ratios (using PAMAM-G4-NH2 (molecular weight=14,215 g/mol, 64 amine end groups), through electrostatic interaction with a ratio of 5:1 having higher encapsulation efficiency (EE%). This complex was tested in mice after Azoxymethane-induced colon adenocarcinoma in comparison to free capecitabine.

The colon tissues of the animals that received capecitabine- PAMAM complex were better than positive control and free capecitabine group. For tumor size, it was 17.6 mm^3, 15.9 mm^3 and 6.8 mm^3 for non-treated, free capecitabine and capecitabine-PAMAM groups respectively. Capecitabine-PAMAM complex also has fewer side effects on blood cell lines and lower liver enzymes levels. The higher effect of the complex is related to higher drug concentration at the tumor site with less drug distribution at other body-organs which decrease the drug side effect. Thus, capecitabine- PAMAM complex could achieve the required drug targeting effect.

Dexamethasone-PAMAM Dendrimer Complexes [86]

The aim of this study was to prepare dexamethasone-PAMAM complexes and investigate the complexation effects on ocular absorption of dexamethasone for diabetic retinopathy (DR). PAMAM was used at different generations (G3 (NH3 ending), G3–OH (-OH ending), G3.5 (-COOH ending), G4 (NH3 ending), G4–OH (-OH ending), and G4.5 (-COOH ending)) at fixed molar ratio to dexamethasone (5:1).

Complex formation between PAMAM and dexamethasone was emphasized by FTIR study which suggested formation of hydrogen bonds between the two compounds. In-vitro release of dexamethasone from the prepared complexes in Phosphate buffer resulted in cumulative percent drug release ranged from about 48% to 73% where G3.5 and G4.5 complex formulations having "-COOH" as

an ending group in their structures showed the highest release rate.

Methyl-thiazol-tetrazolium assay results showed that both anionic dendrimer formulations (with peripheral carboxyl or hydroxyl functional groups) and cationic dendrimers (with amine end groups) have no significant toxicity on human corneal epithelium cells in comparison with dexamethasone solution at a concentration of 1 mg/mL, when incubated for 24 h.

All dexamethasone-PAMAM complexes showed significant higher permeation rate as compared with dexamethasone solution when permeation study was performed on ARPE 19 cell line with PAMAM (G4.5, G4–OH, and G4) showing the highest permeation rates. The study concluded that anionic PAMAMs (with an increase in the number of anionic surface groups) have higher permeation rates over cationic ones which was in contrary with the previously mentioned by Kitchens et al. [87] who reported that cationic, amine-terminated PAMAM G2 exhibited greater permeability than neutral and hydroxyl functionalized PAMAM generations.

In-vivo drug distribution from PAMAM complexes which was done one Sprague–Dawley rats showed that all dexamethasone–PAMAM complex formulations reached higher dexamethason concentrations in the ocular tissues as compared with plain drug suspension after topical application. Anionic dendrimeric formulations showed higher drug concentrations than cationic ones which was in accordance with in-vitro permeation studies.

Enhanced dexamethasone delivery to the ocular tissues from PAMAM complexes can be attributed to enhanced dexamethasone solubility through complexation in addition to the ability of PAMAM dendrimers to cross the cell barriers by both paracellular and transcellular pathways [88].

Dexamethasone was also conjugated to PAMAM G3.5 and PAMAM G4.5 dendrimers with the purpose to prolong the drug presence in retina [89]. The prepared conjugates showed significant prolonged drug release following subconjunctival application than the free dexamethasone. Also, conjugates showed significant lower toxicity compared to dexamethasone itself as the plain PAMAMs showed high cell viability (> 87%).

Simvastatin PAMAM dendrimer complex [90]

Simvastatin is a hypolipidemic drug used to control hyper-cholesterolemia through inhibition of the rate determining step in cholesterol biosynthesis [91]. It is water- insoluble drug having oral bioavailability less than5% [92].

Simvastatine- PAMAM complexes were prepared using PAMAM–G4-NH2, PAMAM–G4-OH and PAMAM–G4-PEG and the effect of PAMAM type and concentration on simvastatin water-solubility and pH-dependent solubility was investigated.

Simvastatin solubility enhancement by complexation with PAMAMs was in the following order: PAMAM–G4-PEG> PAMAM–G4-NH2> PAMAM–G4-OH, with linear correlation between PAMAM concentration and solubility only with PAMAM–G4-PEG. The authors related this to the interaction between simvastatin with the tertiary amino groups and availability of large space for molecular encapsulation and H-bonding. On the other side, FTIR analysis of the resulted complexes emphasized simvastatin formation of amide bond with PAMAM–G4-NH2 while formation of ester bond and hydrogen bonding with both PAMAM–G4-OH and PAMAM–G4-PEG.

In vitro drug release from the prepared simvastatin–dendrimer complexes which was examined using the dialysis tube diffusion method in phosphate buffer pH 7.4 showed that all complexes released the drug in more sustained manner compared to the free simvastatin with initial rapid release for amine and hydroxyl dendrimers up to 3 h followed by slower rat up to 24 h. Although PEG-PAMAM have the highest simvastatin solubility enhancement but it had the slowest rate of drug release compared to NH2 and OH PAMAMs.

Similar results were obtained by Rong et al., [93] who reported that conjugation of simvastatine with Amine-terminated G5 PAMAM dendrimer (G5-NH2) could enhance its solubility and its transepithelial transport of SMV in the Caco-2 cells.

Resveratrol-PAMAM dendrimer complex [94]

Resveratrol is a potent antioxidant provides desirable anti-aging effect when applied topically on the skin. But it suffers from being in-soluble molecules that require to be dissolved in organic solvents which may have harsh effect on the skin. Also, it has some stability issues even in organic solvents [95]. The purpose of this work was to use PAMAM dendrimer ((PAMAM G4) as a carrier for resveratrol to increase its solubility, stability, and penetration through the skin. Resveratrol-PAMAM complex formed through electrostatic interactions, hydrogen bonding and molecular encapsulation. It has enhanced the drug solubility, stability in cream dosage form and increased its penetration and deposition through rat skin layers while no drug was indicated into the receptor compartment of the Franz Diffusion Cells.

CONCLUSION

PAMAM dendrimers by their physicochemical properties represent an excellent promising drug carrier for drug delivery and organ- targeting

purposes. They can enhance drug bioavailability through increasing its solubility, cellular penetration, controlled release of the drug and cell targeting with decreasing its side effects. Although there are stated reports about PAMAMs cellular toxicity, especially cationic ones, but different studies have stated their high biocompatibility and cell viability when used as drug carriers. In addition, PAMAMs have the ability to be structurally modified to diminish their toxic effects. Continues future studies along with in-vivo trials are required to investigate the ability to maximize the benefits of using PAMAMs as drug carriers.

Disclosure of interest

The author reports no conflicts of interest.

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