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Review

Dendrimers: A versatile nanocarrier for drug delivery and targeting

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ABSTRACT

Dendrimers are novel polymeric nanoarchitectures characterized by hyper-branched 3D-structure having multiple functional groups on the surface that increases their functionality and make them versatile and biocompatible. Their unique properties like nanoscale uniform size, high degree of branching, polyvalency, water solubility, available internal cavities and convenient synthesis approaches make them promising agent for biological and drug delivery applications. Dendrimers have received an enormous attention from researchers among various nanomaterials. Dendrimers can be used as a carrier for diverse therapeutic agents. They can be used for reducing drug toxicities and enhancement of their efficacies. The present review provide a comprehensive outline of synthesis of dendrimers, interaction of dendrimer with guest molecules, properties, characterization and their potential applications in pharmaceutical and biomedical field.

1. Introduction

The use of many therapeutic agents is restricted due to their poor solubility, toxicity and stability problems obstructing their clinical application in spite of showing excellent potency (Madaan et al., 2014). Hence, development of delivery system capable of delivering drug efficiently is needed. Many polymers have been demonstrated as drug delivery vehicles traditionally (Brannon et al., 2004); but poorly defined chemical structures (related to the average molecular weight of the polymers and their polydispersity) is a major problem associated with them. Researchers are making attempts to improve on these problems. Researchers have explored nanotechnology to overcome these problems and to improve physicochemical and biological properties of these agents resulting in increased solubilisation, bioavailability, and drug targeting (Gradishar et al., 2005; Ko et al., 2013; Awada, 2014). Many nanoparticle based therapeutic products are available commercially and some are under clinical and pre-clinical trials (Northfelt et al., 1998; Harries et al., 2005). The use of nanotechnology for drug delivery and targeting has proven substantial prospective in improving drug safety and reducing drug-related toxicity. Furthermore, the great concern of scientists in development of a single system capable of delivering therapeutic, targeting and diagnostic agents has directed the design of novel class of nanoparticles as multifunctional platforms (Madaan et al., 2014). Among various nanomaterials, dendritic nanostructures have appealed focus of researchers due to their distinctive physiochemical and structural properties (Lee et al., 2005; Svenson and Tomalia, 2005; Hao-Jui and Jason, 2017).

Dendrimers are well-defined homogenous three-dimensional structure of nanosize comprising of tree-like branches (Srinivasa and Yarena, 2007; Elham et al., 2014). Dendrimers have grabbed a great attention in the field of drug delivery to attain controlled drug delivery and in development personalized medicine systems (Dendrimers, 2017). Vogtle et al in 1978 was the pioneer in making first attempt to design and synthesize dendritic structures (Vogtle et al., 1978). These molecules were originally known as "cascade molecules". After several years of this report, Tomalia's group established a new category of cascade molecules containing amides having relatively smaller structures (Tomalia et al., 1985). Tomalia et al. named these new class of dendritic macromolecules as "dendrimers". The dendrimer name is derived from Greek words "dendros" which means "tree or branch" and "meros" meaning "part" (Madaan et al., 2014; De Brander et al., 1993). At the same time, Newkome's group reported synthesis of analogous macromolecules and named these structures as "arborols", a Latin word "arbor" meaning a "tree".

Dendrimers show characteristics features of both molecular chemistry (due to their step by step controlled synthesis) and polymer chemistry (as it is made up of monomers) (Caminade et al., 2005; Malik et al., 2012). The properties of dendrimers were found to be very different from conventional polymers. In addition, due to their nano-size structure dendrimers extends important applications in the evolving nanomedicine research. They can be used as an efficient delivery system, or carrier system for therapeutic agents (Madaan et al., 2014). VivaGel®, is a first dendrimer-based commercial medical product and many systems are now in clinical trials (Buhleier et al., 1978; Kannan

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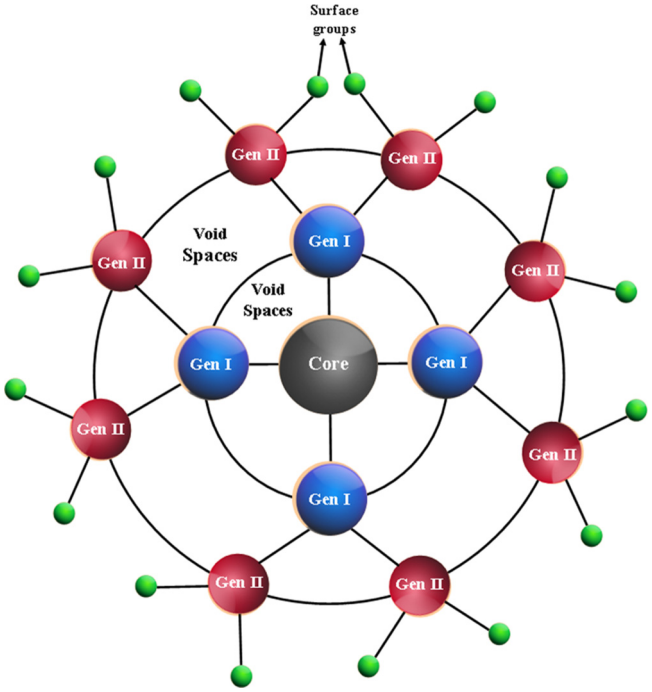

Fig. 1. Schematic representation of dendrimer (Gen = Generation).

et al., 2014). The chemistry of dendrimers is one of the most attractive and rapidly emerging areas of chemistry. The distinctive structure of dendrimers offers diverse prospects for multivalent host-guest interactions (Elham et al., 2014; Boris and Rubinstein, 1996; Spataro et al., 2010).

2. Structure and types of dendrimers

2.1. Structure

Due to well-ordered synthesis and hyper-branched architecture, dendrimers exhibit distinctive features (Caminade et al., 2012). Dendrimers are synthetic nano-architectures nearly 2–10 nm in diameter. They are three-dimensional, hyper-branched and monodisperse structure containing central core surrounded by peripheral groups. The dendrimer typically consists of (a) a central core (single atom or group of atoms), (b) building blocks containing many layers of repeating units known as generations, and (c) numerous functional groups on the surface which play a key role in their properties (Tomalia, 2005; Noriega-Luna et al., 2014) (Fig. 1).

The central core of dendrimers is comprised of an atom or a group of atoms to which branches of carbon and other elements are added through sequence of chemical reaction which is repeated to produce a spherical dendritic structure. However, some of the dendrimers like PAMAM does not have proper spherical structure (Elham et al., 2014; Zimmerman, 1997; Zeng and Zimmrman, 1997). The central core is encircled by extensive branching leading to numerous interior layers containing repeating units. Within the voids of dendrimer building blocks, flexible spaces are formed which facilitates encapsulation of guest molecules. The number of branching points (focal points) from central core to the surface is termed as “generation number” (Tomalia, 2005; Noriega-Luna et al., 2014). For example, a dendrimer holding five branching points is referred as “fifth generation”, denoted as “G5-dendrimer”. Hence, a fifth generation polyamidoamine (PAMAM) dendrimer is denoted as G5-PAMAM. The core part of the dendrimer is sometimes denoted as “zero” generation (G0) and hence does not present focal points in dendrimer structure. The dendrimer “shell” is the region between the focal points (Boas et al., 2006).

The outermost third part of a dendrimer is the surface containing many functional groups which can be tailor-made to interact with the external groups or molecules. The physicochemical properties of dendrimers depends on the branching units and the surface functional group (Semwal et al., 2010; Kalomiraki et al., 2016). The functional groups present at the surface are also called as “terminal group” or “surface group”. For example, a typical dendrimer holding amine functional groups at the surface are called as amino-terminated dendrimers.

During synthesis of dendrimers, increase in each generation (G) approximately doubles the molecular mass of dendritic structure (Hao-Jui and Jason, 2017). The numerous functional groups present at the surface of dendrimers has a vital role in determining their physicochemical properties and biological interactions (Caminade and Turrin, 2014). Hence, chemical alteration of the surface groups can be used for modulating cellular interactions and distributions of dendrimers in biological system (Malik et al., 2000; Hong et al., 2006; Yang et al., 2014; Yang et al., 2012; Hong et al., 2004).

A dendritic structure without a core is named as “dendrons”. A diverse type of dendrimers can be synthesized by connecting two or more dendrons together (Ex. convergent synthesis). A commercially available “Frechet” type of dendrons is demonstrated in the covalent and non-covalent association of dendrimers (Boas et al., 2006; Hawker and Frechet, 1990; Hawker and Frechet, 1990; Hawker et al., 1993).

2.2. Types of dendrimers

2.2.1. Polypropylene imine (PPI) dendrimers

Polypropylene imine (PPI) is the oldest known dendrimer introduced by Vogtle (Buhleier et al., 1978; Vogtle et al., 1978) describing the propylamine spacer moieties. They generally consist of poly-alkylamines with primary amines terminal groups and interior is comprised of several of tertiary tris-propyleneamines. PPI dendrimers have been studied in material and biological sciences. Sometimes “polypropylene amine” (POPAM) and “diamino butane” (DAB) dendrimer names are also used as an alternative term to PPI dendrimers. Polyethylene imine (PEI) dendrimers is a subclass of PPI dendrimers consisting of diaminoethane or diamino propane as functional groups of central core.

2.2.2. Polyamidoamine (PAMAM) dendrimers

PAMAM is a type of dendrimer containing polyamide branches and tertiary amines as branching points. Tomalia and co-workers introduced PAMAM dendrimers in mid-1980s (Tomalia et al., 1985; Tomalia et al., 1984) after which they were studied widely by researchers. “Starburst” dendrimers, a trademark of PAMAM sub-class contains tris-aminoethylene-imine group as a core. The name has been given due to star-like appearance of these high-generation dendrimer structure when observed two dimensionally (2D).

2.2.3. Frechet-type dendrimers

These are the type of dendrimer recently established by Hawker and Frechet (Hawker and Frechet, 1990; Hawker et al., 1993) containing hyper-branched architecture of poly-benzyl ether. Frechet dendrimers contains –COOH groups as the terminal groups and thus offering good branching point for modulation of terminal group functionalization. In addition, the presence of these polar terminal groups helps to enhance solubility of this class of dendrimers in aqueous media and polar solvents (Elham et al., 2014).

2.2.4. Core-shell tecto dendrimer

These are dendritic structures in which dendrimer molecule is used as a core surrounded covalently by shell of other dendrimers. Usually, the generation number of the core is more than the surrounding dendrimers. The attachment of additional shells is controlled by synthetic procedures allowing construction of nanoscale region of 1–100 nm (Li

et al., 1999).

2.2.5. Chiral dendrimers

These dendrimers are synthesized by using constitutionally diverse branches but which are chemically analogous to the chiral core. Chirality is along the axis of the functional groups. Seebach and co-authors (Seebach and Beat, 1998) synthesized chiral dendrimers to study the effect of chiral building blocks on the chirality of dendritic structure and to demonstrate the possibility of enantioselective complexation of host with these architectures. The chirality and hence the optical activity of dendrimers containing only a chiral core reduces with increase in size of the dendrimer. Currently, many scientist are working on the development of chiral dendrimers (Li et al., 1999; Seebach and Beat, 1998; Kremers and Meijer, 1994).

2.2.6. Liquid crystalline dendrimers

The synthesis of liquid crystals has potential industrial applications and has been studied by many researchers. These dendrimers are made up of mesogenic liquid crystalline monomers. These liquid crystalline phases or mesophages are formed by molecules which are usually rod-like (calamitic) or disk-like (discotic) e.g. carbosilane dendrimers having mesogenic functional group such as cyanobiphenyl (Lorenz et al., 1996) and cholesteryl (Frey et al., 1996). The synthesis of the racemic AB2 rod like mesogenic monomer based on conformational isomerism, 13-hydroxy-1-(4-hydroxyphenyl)-2-(4-hydroxy-4″-p-te～-henylyl) tridecan(e5), and preparation of its first four generations of monodendrons and dendrimers using convergent approach is reported by Percec and co-authors (Percec et al., 1995).

Pedziwiatr-Werbicka and co-workers proposed the potential of amino terminated carbosilane dendrimers to deliver short chain siRNA and anti-HIV oligodeoxynucleotide to HIV-infected blood cells. These dendrimers had limited application in the delivery of long-chain double stranded nucleic acids, however the dendriplexes of carbosilane dendrimers and anti-HIV nucleic acid were stable and less cytotoxic to blood cells than the plain dendrimers signifying their utility in the delivery of bioactives (Pedziwiatr-Werbicka and Fuentes, 2013; Jorg et al., 1994).

2.2.7. Peptide dendrimers

These are the radial or wedge-like branched macromolecular structures comprised of peptidyl branching core and covalently bonded terminal functional groups. The peptide dendrimers are frequently synthesised by divergent and convergent method of synthesis. They have been studied for several biotechnological and biochemical uses due to explicit composition and ease of synthesis. Peptide dendrimers find their application as surfactants and in biomedical field as multiple antigen peptides (Sadler and Tam, 2002), protein mimics (Kinberger et al., 2002) and carrier for drug and gene delivery (Sadler and Tam, 2002; Kinberger et al., 2002). Darbre and Reymond have used peptide dendrimers as esterase catalysts (Darbre and Reymond, 2006).

2.2.8. Multiple antigen peptide dendrimers

Multiple antigen peptide (MAP) dendrimer was reported by J.P. Tam (Tam, 1988) which are constructed using polylysine skeleton. The branching points in the structure of dendrimer are introduced using monomer unit of alkyl amino side-chain of lysine. MAP dendrimer has been studied widely in biomedical research including vaccine and diagnostic research (Tam et al., 2000).

2.2.9. Glycodendrimers

Glycodendrimers are monodispersed macromolecular dendritic structure containing carbohydrate moiety (Boas et al., 2002; Choi et al., 2000). Most of the glycodendrimers contains saccharide residues as terminal groups and a sugar unit as the central. Carbohydrate cantered, carbohydrate-based, and carbohydrate-coated dendrimers are three categories of glycodendrimers (Nanjwade et al., 2009; Woller and Cloninger, 2001). These dendrimers show better association with lectins attached systems than mono-carbohydrate attached systems (Roy and Baek, 2002; Oliveira et al., 2010). They are used in site-specific drug delivery to the lectin-rich organs.

2.2.10. Hybrid dendrimers

Hybrid dendrimers is a blend of linear and dendritic polymers and present in the form of hybrid block or graft copolymer. Dendritic hybrids are likely to form due to the spherical shape and large number of terminal functional groups of dendrimers. Association of the small dendritic fragment to the various reactive chain ends offers them for several application including surface active agents, adhesives or compatibilizers, or hybrid dendritic linear polymers. The dendritic hybrids has a compact, rigid, uniformly shaped globular structure, which have been explored for various aspects in the field of drug delivery (Roy et al., 1993; Pushechnikov et al., 2013; Kesharwani, 2014).

2.2.11. Polyester dendrimers

Development of therapeutic index of drugs is an important area in disorders like cancer, inflammatory and other infectious diseases like HIV. Polyester dendrimers is very hopeful in this area due to its biocompatible and biodegradable properties. Because of diminished exposure of drug to healthy tissue, they exhibit low toxicity than other dendrimers which is a desired property from any molecules as drug delivery systems. These dendrimers have interior void spaces analogous to common dendrimers and therefore they can be used to as a carrier for small molecule drugs, metals, or imaging moieties (Jean-d'Amour and Twibanire, 2014; Gillies et al., 2005; Morgan et al., 2003; Antoni et al., 2009; Jain et al., 2010). The reactive surfaces of polyester dendrimers can be altered to achieve drug targeting, improved bio-distribution, and modulation of drugs release (Lee et al., 2005; Lee et al., 2006). The representative structures of various types of dendrimers is depicted in Fig. 2.

3. Synthesis

Dendrimers are related to molecular chemistry due to their step-by-step controlled synthesis and because of their repetitive structure made of monomers they belong to polymer chemistry. Dendrimers are synthesized using either a divergent method or convergent methods (Elham et al., 2014).

3.1. Divergent synthesis

The divergent synthesis involves construction of the dendrimer starting from the core and building up the molecule towards the periphery in a stepwise manner using two basic operations. In each step a new layer of branching unit is added which causes increase by one generation number in the structure of dendrimer. In the first operation, monomer is coupled and later the monomer end-group is deprotected or transformed to create a new reactive surface and then coupling of a new monomer, etc. It is ascending synthesis of dendrimers. Inspite of being simple, this approach requires very effective reactions to circumvent errors in the dendrimer structure because increasing number of reactions must take place concurrently with increasing generations. Several dendritic structures can be built with divergent methods viz. poly (amidoamine) dendrimers (PAMAM), poly (propylene imine) dendrimers (PPI), and phosphorus-based dendrimers (Newkome et al., 1991).

The divergent method of dendrimer is associated with two main problems. Firstly, the number of reaction points rises speedily during the synthesis which causes increase in reaction points and corresponding increase in molecular weight. This leads to slower reaction kinetics and thus making difficult to create higher generation dendritic network. Consequently, this leads to increasing deletions during the growth of the dendrimer causing numerous of defects in the higher

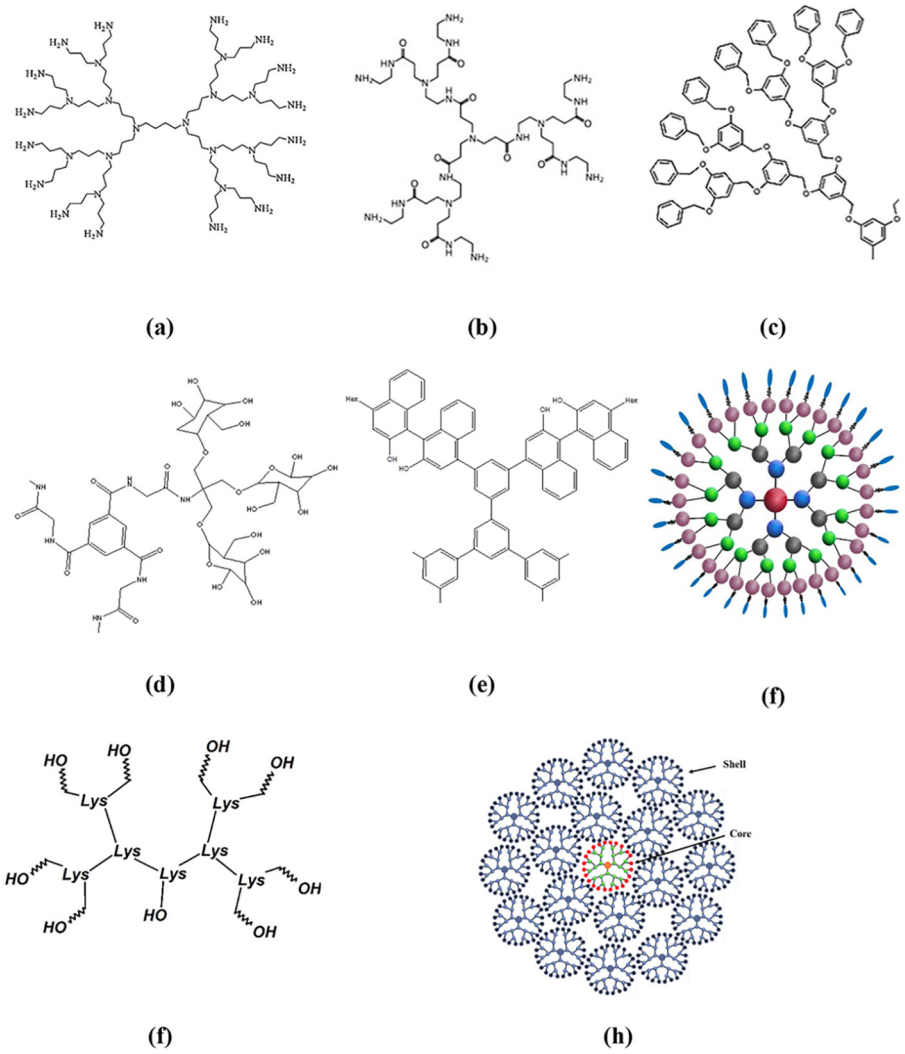

Fig. 2. Structures of (a) Poly (propylene imine) (PPI) G3 dendrimer, (b) Polyamidoamine (PAMAM) dendrimer, (c) Frechet-type dendrimers, (d) Glycodendrimers, (e) Chiral dendrimer, (f) Liquid crystalline dendrimers, (f) Multiple antigen peptide dendrimers, and (h) Core-shell tecto dendrimers.

generation dendrimer product. Secondly, the separation of the desired product from reactants or "deletion products" becomes challenging due to high molecular similarity between desired and by-products. Regardless of these drawbacks the divergent approach has been functional in the synthesis of diverse dendrimer designs (Boas et al., 2006).

3.2. Convergent synthesis

In contrast to divergent synthesis, the convergent method starts at the periphery and proceed towards the core by mostly one-to-one coupling of monomers. A small dendron is formed in the beginning by linking two groups at periphery to a branching unit. Later, two of these dendrons is linked to branching unit to form a higher generation dendron. This coupling process can be continued causing doubling the size of dendron each time. In the final part of the convergent synthesis, core is formed in the end and two or more dendritic segments (dendrons) are joined together at the core leading to formation of dendrimer. In convergent approach, structural defects can be certainly circumvented since the number of reacting partners does not change on increasing generation. The number of reactive sites remains minimal during the convergent production process which leads to faster reaction rates and yields. It is descending synthesis of dendrimers. However, major limitation of this method is that it gives low yield in the synthesis of higher generation dendrimers and hence preferred for the synthesis of lower generation dendrimers. Dendritic structure prepared by convergent methods is poly (aryl ether) framework (Frechet-type) (Madaan et al., 2014; Hawker and Frechet, 1990; Newkome et al., 1991). The schematic representation of divergent and convergent methods of synthesis of dendrimers is shown in Fig. 3.

3.3. Hypercores and branched monomer growth

The oligomeric moieties are previously assembled and then can be linked together to form dendrimers in relatively few steps with higher yields (Nanjwade et al., 2009). The schematic representation of hypercores and branched monomer growth is given in Fig. 4.

3.4. Double exponential growth

It is almost same as the rapid growth technique for linear polymers. In this method, the monomers for divergent and convergent growth are prepared from a single starting material. The resulting two products are then reacted together to give orthogonally protected trimer. This trimer is then used for repeating the growth of dendrimer. Due to fast synthesis feature of double exponential growth approach, it can be easily coupled with divergent or convergent growth (Juris, 2003). The double exponential growth scheme is depicted in Fig. 5.

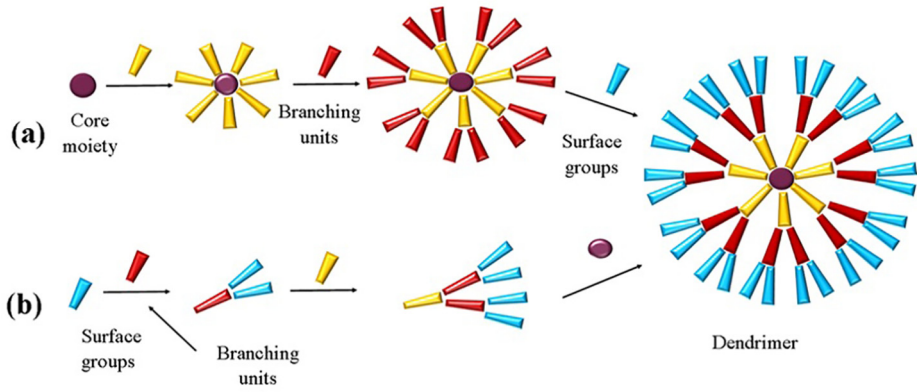

Fig. 3. Schematic representation of (a) Divergent synthesis and (b) Convergent methods of synthesis of dendrimers.

3.5. Lego chemistry

In lego chemistry, cores and branched monomers having more functional groups are used to prepare phosphorous dendrimers. After few variations in general synthetic preparation scheme, the established scheme permits proliferations of the number of surface groups of dendrimer from 48 to 250 in a single step. Minimum requirement of solvent, facile purification possibility and formation of environmentally caring by-products such as water and nitrogen are the key features of this technique (Kawaguchi et al., 1995).

3.6. Click chemistry

"Click" chemistry is one of the important high yielding reactions. Hence, this technique has been used in synthesis of many new dendritic structures. The tactic is to build carbon-rich dendrimers and environmental friendliness. Copper-assisted azide-alkyne cycloaddition (CuAAC) (Rostovtsev et al., 2002), thiol-yne click reactions (TYC) (Hoogenboom, 2010; Lowe et al., 2010; Cervera-Procas et al., 2013), and thiol-ene click reaction (TEC) (Lowe, 2010; Lowe and Harvison, 2010) reaction are some of the mostly used click reactions in the synthesis of dendrimer.

Apart from these reactions, new reactions are being explored to further improve the dendritic architecture (Svenson and Tomalia, 2012). Staudinger reaction was modified to give it "click" elements (Majoral et al., 2002). An "onion peel" and a "Janus" dendrimer (Gottis et al., 2013) were built with this new reaction. Trans-cyclooctene/tetrazine (Katir et al., 2015) pair and Sharpless' new SuFEx reaction (Karver et al., 2012) are some of the other reactions that exhibits click characteristics and could be used for dendrimer synthesis. Hoogenboom have also studied other prospective click reactions (Dong et al., 2014; Becer et al., 2009). Mullen et al coupled folic acid conjugated dendrimer with a fluorescein isothiocyanate conjugated dendrimer and demonstrated their receptor mediated targeting and fluorescence imaging properties. These dendritic units were coupled by using 1,3-dipolar cycloaddition reaction (click chemistry) between an alkyne and azide surface groups of first dendrimer and second dendrimer, respectively. In the *in vitro* study carried out on human epithelial cancer cell line, it was found that this coupled dendrimer module precisely target the over-expressed folic acid receptor (Arseneault et al., 2015).

4. Dendrimer-drug interaction

The interaction of guest molecule with dendrimer is mainly through interaction with the exterior surface of dendrimers. The dendrimer structure decides the type and number of guest molecules that can be incorporated into or complexed with dendrimers. The loading potential of dendrimers can be considerably enhanced by modulating the association of guest with several terminal groups of the dendrimer. The availability of terminal groups for interactions with the guest molecules increases proportionately with generation number of dendrimer (Mullen et al., 2011). The various modes of interaction of drug with dendrimer are discussed below and represented in Fig. 6.

4.1. Electrostatic interactions

When the molecular groups present on the surface of the dendrimer are charged, the surface may electrostatically attract oppositely charged molecules. Range of ionizable drugs or molecules can be attached electrostatically to dendrimers due to numerous ionisable groups present on the dendrimer surface. This enables the resulting complex to exhibit adequate solubility in water. For example, electrostatic

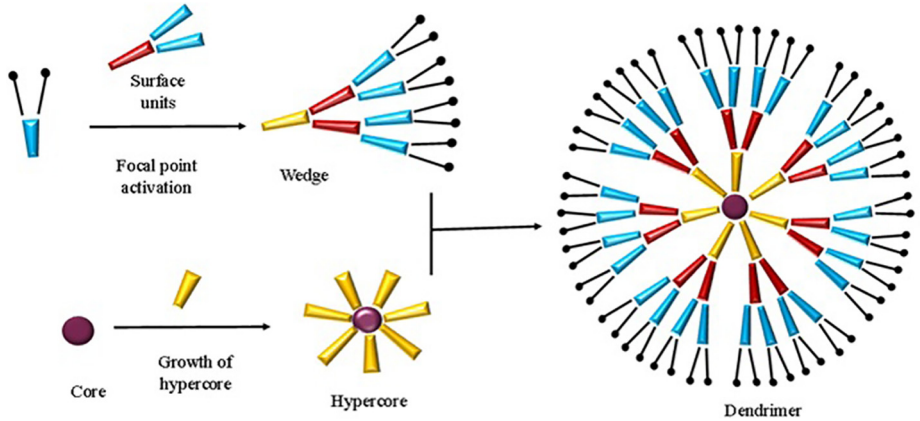

Fig. 4. The schematic representation of Hypercores and Branched Monomer Growth.

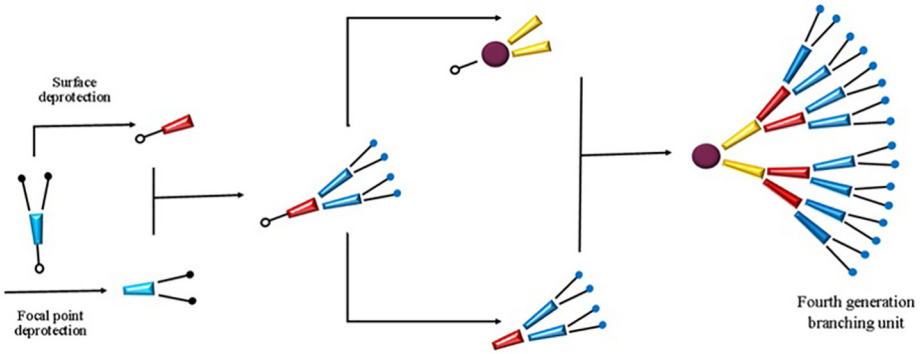

Fig. 5. Schematic representation of double exponential growth.

interaction can occur between amine groups of PAMAM dendrimers and carboxyl groups of ibuprofen. It has been estimated that, at pH 10.5 about 40 ibuprofen molecules is conjugated with G4 PAMAM dendrimer resulting in substantial increase of solubility of ibuprofen (Wang et al., 2012a,b). Many other drugs like indomethacin (Kabanov et al., 1998), ibuprofen (Chauhan et al., 2003), and benzoic acid (Kolhe et al., 2003) have been demonstrated to interact electrostatically with different dendrimers to form stable complexes.

4.2. Conjugation of drug to dendrimer

Drug can be attached to dendrimer covalently or non-covalently. The covalent bonding of drugs to the terminal groups of dendrimers can be done with some chemical inserts like polyethyleneglycol (PEG), p-amino benzoic acid, etc. The linkages like amide or ester provides stability and better controlled drug release. Yang and Lopina demonstrated the conjugates of penicillin V (XII) with G3 and G2.5 PAMAM dendrimers through ester and amide linkages, respectively using PEG spacer. Authors reported that the ester linkage between drug and dendrimer provided controlled drug release, whereas amide linkage resulted in improved bond stability (Beezer et al., 2003). Pasut et al. (2005) developed epirubicin prodrug by preparing its conjugate with PEG dendrimers using aminoadipic acid as branching molecules. These conjugated system showed improved blood residence time and better therapeutic action. An improved stability of bound drug toward chemical degradation was also observed (Yang and Lopina, 2003).

4.3. Encapsulation of drugs within the dendritic architecture

Due to open nature of dendritic architecture, encapsulation of drug molecules within the branches of a dendrimer is possible. Physical entrapment or non-bonding interactions with specific structures of the dendrimer can be used as encapsulation methods for drugs (Pasut et al., 2005).

4.4. Unimolecular micelles

Unimolecular micelles are the dendrimers consisting of hydrophobic core surrounded by a hydrophilic shell. Due to the covalent connection of the hydrophobic segments, micellar structure is maintained at all concentrations (Madaan et al., 2014; Maciejewski, 1982).

5. Mechanism of drug delivery through dendrimers

Due to the definite 3D structure and several surface functional groups, dendrimers can act by encapsulation of drugs within the dendritic structure or by forming electrostatic/ covalent bonds between drugs with terminal functional groups of dendrimers. Two mechanisms of the drug delivery from drug-dendrimer conjugate have been reported in the literature. The first mechanism is owed to *in vivo* cleavage of covalent bonds between drug and dendrimer in existence of enzymes or an environment required for bond breaking. The second mode of drug release is the alteration in physical conditions temperature and pH which are not dependent on external factors (Tomalia et al., 1985; Hawker and Frechet, 1990; Tomalia et al., 1984; Tripathy and Das, 2013).

6. Biocompatibility of dendrimers

The biocompatibility of dendrimer is very important when it is considered for medical applications. The dendrimers should be non-toxic and non-immunogenic when used in drug delivery applications. Dendrimers possessing positively charged surface groups causes destabilization of cell membranes leading to cell lysis. The cytotoxicity potential of dendrimers is seen to be generation dependent, wherein higher generation dendrimers have high toxicity than the lower generations (Zinselmeyer et al., 2002). The PAMAM dendrimers with amino surface groups possesses lesser cytotoxicity than the amino terminated linear polymer. The lesser extent of cytotoxicity of PAMAM dendrimer can be ascribed to lesser adherence of the globular

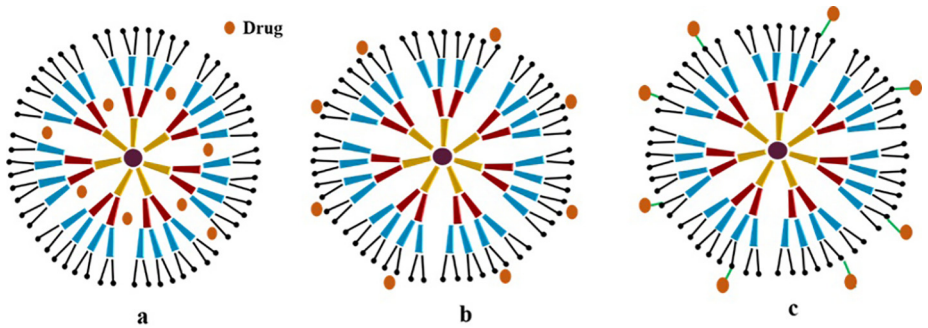

Fig. 6. Representation of various ways of interaction of drug with dendrimers (a) physical entrapment of drugs in dendrimer structure, (b) adsorption of drug molecules on the surface of the dendrimer via intermolecular interaction, and (c) conjugation of drug molecules to the surface groups of dendrimer.

dendrimers to cellular surfaces. The type of amine functionality and the degrees of substitution in the dendrimer structure are the factors determining cytotoxicity potential where secondary or tertiary amines being lesser toxic than the primary. The haemolytic effects and generation dependent cytotoxicity of PPI dendrimers with amine terminal groups are similar to that of PAMAM dendrimers. In addition to surface groups of dendrimers as a determinant of biocompatibility, it has been studied that the aromatic interior may cause haemolysis via hydrophobic membrane contact (Yoo et al., 1999). The biocompatibility of the dendrimers can be improved by surface modification of dendrimer by using PEG (Frechet and Hawker, 1996).

7. Biosafety of dendrimers

It has been established that the cationic macromolecules interact with negative biological membranes resulting in destabilization and cell lysis (D'Emanuele and Attwood, 2005; Fischer et al., 2003). Dendrimers with cationic surface groups also have a tendency to interact with lipid bilayer which leads to weakened integrity of biological membrane and augmented permeability. This interaction eventually may cause leakage of cyotosolic proteins (like lactate dehydrogenase and luciferase) followed its disruption and cell lysis (Rittner et al., 2002; Chen et al., 2004; Mecke et al., 2005). PAMAM dendrimers are shown to cause concentration and generation dependent cytotoxicity and hemolysis due to the positively charged amino groups on PAMAM surface, thus limiting its potential applications in pharmaceutical and biomedical fields (Kesharwani, 2014; Domanski et al., 2004; Kukowska-Latallo et al., 2005).

In a study carried out by Jevprasesphant et al to demonstrate the cytotoxicity of PAMAM dendrimers using Caco2 cells, it was observed that the anionic or half generation dendrimers have considerably low toxicity compared to cationic family of the same dendrimer (Gothwal et al., 2015).

Similar type of observations were observed in the study carried out by Jones et al. They carried out nanotoxicological studies on amine terminated PAMAM dendrimers and it was found that the intravenous administration to mice was lethal and produced disseminated intravascular coagulation like condition. In a further investigation carried out using flow cytometry and microscopic analysis, it was confirmed that platelet disruption was caused by cationic fluorescein isothiocyanate labeled G7 PAMAM, however, carboxyl terminated (anionic) and hydroxyl terminated (neutral) PAMAM dendrimers did not cause in change their function or morphology of platelet (Jevprasesphant et al., 2003).

To overcome the toxicity issues and make dendrimer biocompatible, various approaches like modification of surface groups have been reported in order to reduce cytotoxicity and improve the pharmacokinetic profile of dendrimers (Yoo et al., 1999). Two approaches are being proposed to overcome the *in vitro* toxicity problems of dendrimer (a) synthesis of biocompatible or biodegradable dendrimers (neutral and anionic) like polyether, polyester or polyetherimine, polyether copolyester, phosphate, citric acid, melamine, peptide or triazine dendrimers and (b) the peripheral positively charged groups can be masked by acetylation and PEGylation (Jain et al., 2010).

8. Applications

Dendrimers have a number of advantages as they can be used as carriers or scaffolds for diagnosis and therapy. In addition, dendrimers are monomolecular polymer micelles and this property avoids the instability of drug formulation. On the other hand, due to variable generation size of dendrimers they can be selected for a suitable biomedical applications.

8.1. Cancer therapy

Drug molecules can be covalently attached to the dendrimer periphery due to their well-defined multivalency. This approach is used to develop dendrimers as an anticancer agents. Paclitaxel, an anticancer drug is a poorly soluble. The conjugates of Paclitaxel with PAMAM G4 dendrimer with hydroxyl terminated groups and bis (PEG) polymer were studied for solubility and cytotoxicity enhancement. The conjugates showed 10-fold increase in cytotoxicity than the free non-conjugated paclitaxel (Jones et al., 2012; Khandare et al., 2006).

Shukla et al studied the human growth factor receptor-2 (HER2) specific tumor targeting efficiency of anti-HER2 mAb (monoclonal antibody) by preparing its conjugate wit PAMAM G5 dendrimer. The dendrimer-antibody conjugate showed rapid and efficient cellular internalization without variations in specificity of targeting during internalization process and blocking experiments with free antibody. Targeting of HER2-expressing tumors was also observed by the conjugated antibody in the animal studies (Shukla et al., 2008).

Chittasupho and co-authors investigated the effectiveness of PAMAM dendrimers conjugated doxycycline on cellular binding, cytotoxicity, and migration of BT-549-Luc and T47D breast cancer cells was studied. The dendrimers conjugated with drug was surface functionalized with LFC131 peptide having potential to recognize CXCR4 expressed on the surface of breast cancer cells. The LFC131-DOX-D4 showed substantially improved *in vitro* cellular toxicity as compared with non-targeted dendrimers and reduced migration of BT-549-Luc breast cancer cells toward chemoattractant (Chittasupho et al., 2017).

In a study carried out by Nguyen et al., four different pluronics namely, P123, F68, F127 and F108 were conjugated on PAMAM G4. A hydrophobic drug fluorouracil (5-FU) was used as a model drug. PAMAM G4 conjugated with the highly lipophilic pluronic P123 showed higher drug loading efficiency compared to other pluronics. The drug-loaded dendrimer showed higher anti-proliferative activity against MCF-7 breast cancer cell. This study demonstrated the potential of highly lipophilic pluronics-conjugated nanocarriers in delivery of hydrophobic drugs (Nguyena et al., 2017).

The delivery of active constituents from natural sources through dendrimers have been demonstrated by many researchers. Berberine, a nitrogenous cyclic natural alkaloid exhibiting potential anticancer activity is less explored because of poor pharmacokinetic behaviour. Gupta et al studied G4 PAMAM conjugated berberine as an encapsulation approach for delivery of barberine. The results of MTT assay revealed significantly higher anticancer activity for the PAMAM-berberine conjugate against MCF-7 and MDA-MB-468 breast cancer cells. In addition, the conjugates were considerably safe and biocompatible. The *in vivo* studies carried out in albino rat model showed significant enhancement in PK parameters (half-life and AUC) of berberine (Gupta et al., 2017).

Another natural bioactive cytosine arabinoside (Ara-C), a nucleoside analog having potential anticancer activity has restricted efficacy owed to drug resistance, inadequate uptake and accumulation of drug inside the cancer cells. Szulc and co-workers studied the Ara-C triphosphate (Ara-CTP) encapsulated in 4th generation maltose-modified poly (propylene imine) glycodendrimers (PPI-m OS) for leukaemia treatment. The cytotoxicity and apoptosis results revealed improved activity of Ara-CTP dendrimers conjugate compared to free Ara-C and Ara-CTP against 1301 leukemic cells. It was concluded by the authors that, the enhanced uptake and cytotoxicity of Ara-CTP-dendrimers with blocked human equilibrative nucleoside transporter (hENT1) could be used for chemotherapy against resistant acute lymphoblastic leukaemia cells with lower expression of hENT1 (Aleksandra et al., 2016).

8.2. Gene, protein and enzyme delivery

The transfer of genes through the cell membrane into the nucleus takes place via vectors. Research is being carried out to use dendrimers

as vectors without damaging or deactivating the DNA. PAMAM dendrimers have been tested as vectors used in gene therapy. They have amino groups on the surface which interacts with phosphate groups of nucleic acids ensuring formation of transfection complexes. Further, the activated dendrimers have ability to carry a higher amount of genetic material compared to that of viruses (Klajnert and Bryszewska, 2001).

Lakshminarayanan A and co-authors studied a poly propyl ether imine (PETIM) containing nitrogen core dendrimer for DNA complexation efficacies and gene delivery vector properties. A quantitative luciferase assay revealed 100 times higher gene transfection compared to poly (ethylene imine) branched polymer containing same number of cationic sites as the dendrimer (Lakshminarayanan et al., 2013).

Due to the poor bioavailability of siRNA, the delivery of siRNA to the lungs via intravenous route is challenging. Further, the formulation and maintenance of activity of free siRNA after its delivery to the lungs using inhalation devices is also difficult. Bielski E et al investigated the potential of a triphenylphosphonium (TPP) modified PAMAM G4 dendrimer (G4NH2-TPP) to increase the *in vitro* transfection efficiency of siRNA. The conjugate containing 12 TPP molecules on the surface complexed with siRNA (dendriplexes) showed highest *in vitro* gene knockdown efficiency. To demonstrate the efficiency of TPP-dendriplexes for pulmonary use, mannitol microparticles containing 12 TPP-dendriplexes were developed. This showed deep lung deposition for formulations without any influence on the *in vitro* gene knockdown efficiency of the siRNA (Bielski et al., 2017).

The possibility of increasing the performance of relatively large therapeutic molecules like proteins have been explored by Wang X et al. A series of conjugates comprising therapeutic protein, streptokinase (SK) and PAMAM G3.5 dendrimers were prepared by active ester method in various molar ratios. Among the various rations of SK and PAMAM, the conjugate of equimolar (1:1) ratio showed highest enzymatic activity retention (80% retained). The SK-PAMAM conjugates prepared in higher molar ratios (1:10 and 1:20 of SK: PAMAM) showed lower initial enzymatic activities, whereas, sustained thrombolytic activity in plasma. Thus the high enzymatic activity obtained in this study proposes a possible application of dendrimers for modifying many bioactive macromolecules (Wang et al., 2007).

8.3. Solubility enhancement of poorly soluble drugs

Dendrimers having hydrophobic core and hydrophilic surface can be used as solubility enhancers of poorly soluble drug by covalent and non-covalent complex formation. Hydrophobic core can encapsulate hydrophobic drug and hydrophilic drugs can be conjugated with the multivalent surface. Tekade and co-authors have reported encapsulation of methotrexate into the hydrophobic core and all-trans retinoic acid were entrapped inside the small voids of branching clefts. The electrostatic interactions between the carboxyl groups of the drug and the amine surface groups of the dendrimers improved the stability of loaded drug and showed pH-dependent drug-release (Tekade et al., 2008). Researchers have also utilized PEGylated dendrimers to achieve higher solubility and biocompatibility.

8.4. Dendrimer for drug delivery and targeting

Dendrimers have been demonstrated as ideal carrier for the delivery and targeting of therapeutic and diagnostic agents due to distinctive properties of dendrimers like monodispersity, adjustable surface functionality and internal cavities. The important features of dendrimers which makes them a potential drug carrier comprise their excellent uptake by cells, multiple functionalities and capability to conjugate or include high molecular weight substances, improved circulation time. In addition, dendrimer nanostructures facilitates the passive targeting of drugs to tumour tissues via enhanced permeation of these macromolecules (Kumar et al., 2015; Saovapakhiran et al., 2009; Najlah et al., 2007).

They have an enhanced permeability and retention effect that makes them the agent for targeted drug delivery. In a permeability study carried out by Kitchens et al using cationic PAMAM-NH2 (G0-G4) dendrimers on Caco-2 cell, it was suggested that the PAMAM dendrimers having amine terminal groups could cross the biological membranes probably by paracellular and endocytosis pathways (Kitchens et al., 2005). The drug targeting property of folic acid (FA) conjugated G5-PAMAM dendrimer was demonstrated by Patri et al using methotrexate as model drug. A receptor mediated drug delivery demonstrating high specificity for KB cells with slower drug release was reported (Patri et al., 2005).

Because of suitable structural properties and controlled size of dendrimers, they have become interesting material for biochemical applications. Recently, researchers have combining the characteristics properties of dendrimer with the magnetic nanoparticles (MNPs) to achieve improved therapeutics and biomedical applications (Asghar et al., 2017).

8.4.1. Transdermal drug delivery

Transdermal drug delivery has been useful to overcome GI and renal side effects of NSAID's and also shows extended drug release. Dendrimers have been studied by various researchers for applications in transdermal drug delivery systems. Chauhan and co-authors studied the transdermal permeation of indomethacin by using PAMAM dendrimers as drug delivery vehicles (Kawaguchi et al., 1995).

Manikkath J et al studied the combined effects of arginine terminated peptide dendrimers and low frequency ultrasound on the transdermal permeation of ketoprofen. The combination of peptide dendrimer and ultrasound application gave synergistic effect. Higher plasma concentration of drug was observed during *in vivo* studies compared to passive diffusion. Transdermal administration of ketoprofen with dendrimer showed similar absorption and plasma drug levels with oral route (Manikkath et al., 2017).

8.4.2. Oral drug delivery

Oral route administration is preferred because of the patient compliance. Generally, for anticancer agents oral route is preferred as it reduces the cost of administration and also facilitates the use of more chronic treatment regimes. However, poor aqueous solubility and permeability across the biological membrane of drug limits its intake through oral route (Csaba et al., 2006; Malingre et al., 2001). This drawback associated with the drug is overcome by the usage of dendrimers as the drug delivery vehicles giving promising results. The permeation of PAMAM dendrimers and surface modified PAMAM dendrimers across the Caco-2 cell monolayers was studied by Jevprasesphant et al and concluded that PAMAM dendrimers and surface modified PAMAM dendrimers with lauroyl groups could efficiently traverse epithelial monolayers via paracellular and transcellular pathways (Gothwal et al., 2015). Later, propranolol-PAMAM dendrimer conjugate was investigated for transport across Caco-2 cell monolayers and it was observed that the conjugate could reduce the effect of P-glycoprotein on intestinal absorption of propranolol. Hence, it was concluded that dendrimers can bypass P-glycoprotein efflux transporter and can facilitate the oral administration of drugs (D'Emanuele et al., 2004). Najlah et al investigated the oral delivery of prodrug of naproxen which has low aqueous solubility based on PAMAM dendrimers. Authors investigated the transepithelial permeability of naproxen-dendrimer conjugates and stability of these conjugate was investigated in 50% liver homogenate and 80% human plasma. Two different linkers i.e. lactate ester and diethylene glycol were used to bond drug to dendrimer and these linkages showed considerable effect on the stability of conjugate. Conjugates with lactate ester linker were more stable in plasma and demonstrated the slow hydrolysis in liver homogenate. Whereas, diethylene glycol linker based conjugate demonstrated the high chemical stability with quick release of drug in plasma and liver homogenate. Finally, authors concluded that the dendrimer based

Table 1
Applications of dendrimers in drug delivery.

Dendrimer type	Drug Molecule	Therapeutic purpose	Reference
PAMAM	Paclitaxel	Cancer	Khandare et al., 2006
PAMAM	Anti-HER2 mAb (monoclonal antibody)	Cancer	Shukla et al., 2008
PAMAM	Doxycycline	Cancer	Chittasupho et al., 2017
PAMAM	Berberine	Cancer	Nguyena et al., 2017
PAMAM	5-Fluorouacil	Cancer	Buczkowski et al., 2011
PEGylated-PAMAM	5-Fluorouacil	Cancer	Bhadra et al., 2003
PAMAM	Methotrexate	Cancer	Zhang et al., 2011
PAMAM	Methotrexate	Cancer	Quintana et al., 2002
PAMAM	CDDP	Cancer	Kirkpatrick et al., 2011
PAMAM-COOH	Cisplatin	Cancer	Yellepeddi et al., 2011
PAMAM	Tamoxifen	Cancer	Li et al., 2013
PAMAM	Flurbiprofen	Inflammation	Asthana et al., 2005
PAMAM	Cisplatin	Cancer	Malik et al., 1999
PAMAM	Indomethacin	Inflammation	Chauhan et al., 2004
PAMAM	DNA	Cancer	Urbiola and Sanmartin, 2014
PAMAM	Methotrexate and all-trans retinoic acid	Cancer	Tekade et al., 2009
PAMAM	DNA	Inhibition of tumor growth and angiogenesis	Vincent et al., 2003
PAMAM	Pilocarpine nitrate and tropicamide	Miotic activity and mydriatic activity	Jiao et al., 2008
PAMAM	Glucosamine and glucosamine-6-sulfate	Immunology and angiogenese	Shaunak et al., 2004
PAMAM	Fluocinolone	Inflammation	Iezzi et al., 2012
PAMAM	CAT reporter transgene	Skin gene transfections	Bielinska et al., 2000
PAMAM	Ketoprofen and Diflunisal	Improve oral bioavailability and inflammatory	Cheng et al., 2007
PAMAM	8-Methoxypsiralene	Hyperproliferative skin disease	Borowsk et al., 2010
PAMAM	Riboflavin (B2 vitamin)	Dermatological indication	Filipowicz and Wolowiec, 2011
PAMAM	Propanolol	Improve oral bioavailability	D'Emanuele et al., 2004
PAMAM	5-Aminosalicylic acid	Improve oral bioavailability	Wiwattanapatapee et al., 2003
PAMAM	Ketoprofen	Inflammation	Na et al., 2006
PAMAM	Chlorambucil	Cancer	Hui et al., 2005
PAMAM	siRNA	Cancer	Patil et al., 2008
PAMAM	Cisplatin and siRNA	Cancer	Zheng et al., 2014
PAMAM	siRNA	Cancer	Liu et al., 2014
RGD modified PAMAM	Doxycycline	Cancer	Zhang et al., 2011
PAMAM-mPEG-PDEA	5-Fluorouacil	Cancer	Jin et al., 2011
PEGylated-PAMAM	Doxycycline	Cancer	Zhu et al., 2010
EGF-PAMAM	Boron	Boron neutron capture therapy	Yang et al., 1997
Folic acid-PAMAM	Methotrexate	Cancer	Haandel van and Stobaugh, 2010
PEGylated-PAMAM	Methotrexate	Cancer	Singh et al., 2008
Fatty acid and phospholipid-PAMAM	5-Fluorouracil	Cancer	Tripathi et al., 2002
Cyclodextrin(α-CDE conjugate)-PAMAM	DNA	Spleen, liver and kidney targeting	Kihara et al., 2003
Mannosylated-PAMAM-α-cyclodextrin	DNA	Kidney targeting	Wada et al., 2005
PPI	Methotrexate	Cancer	Birdhariya et al., 2015
PPI	Doxycycline	Cancer	Gupta et al., 2010
PPI	Paclitaxel	Cancer	Kesharwani et al., 2011
PPI	Methotrexate	Cancer	Kurmi et al., 2011
PPI	Methotrexate, DOX	Cancer	Wang et al., 2012a
PPI	siRNA	Cancer	Taratula et al., 2009
PPI	DNA	Liver targeting	Dufes et al., 2005
PPI	Collagen	Artificial biomaterial	Duan and Sheardown, 2006
PPI-m	Cytarabine (Ara-C)	Cancer	Aleksandra et al., 2016
Polysorbate-PPI	Docetaxel	Brain cancer	Gajbhiye and Jain, 2011
PEGlyated PPI	DNA	Effective transfection agents	Tack et al., 2006
PLL	5-Fluorouacil	Cancer	Zhao et al., 2014
PLL	DNA	Cancer	Ma et al., 2013
PLL	Doxorubicin	Cancer	Jain et al., 2014
PLL	Doxorubicin	Cancer	Niidome et al., 2014
Polyether-co-polyester	Methotrexate	Cancer	Dhanikula et al., 2008
Polyster	Doxycycline	Cancer	Morgan et al., 2006
Polylysine dendrimer	Doxorubicin	Cancer	Kaminskas et al., 2011
Phosphorus dendrimers	Carteolol	Hypertension	Spataro et al., 2010
PEGylated-PLL	Camptothecin	Cancer	Fox et al., 2009

Abbreviations: EGF, epidermal growth factor; PAMAM, polyamidoamine; PEG, poly (ethylene glycol); PLL, poly-L-lysine; PPI, polypropyleneimine.

conjugate of naproxen could enhance the oral bioavailability and conjugate based on lactate ester linker may serve as promising candidate for controlled release (Najlah et al., 2007). Conjugate of anticancer drug 7-ethyl-10-hydroxy-campothecin (SN38) with 3.5G PAMAM dendrimers showed improved oral bioavailability with reduced toxicity (Goldberg and Vijayalakshmi, 2011).

8.4.3. Ocular drug delivery

The topical application of drugs is necessary for the treatment of ocular disorders. Most of the times intraocular delivery have poor bioavailability problems due to elimination of formulation by tear turnover or nasolacrimal duct mediated drainage of fluid in excess. Also, formulation that is to be applied by ocular route should be isotonic, non-sensitizing, biodegradable, non-irritating, and biocompatible with good retention within the eye (Nanjwade et al., 2009; D'Emanuele et al., 2004). Dendrimers have been used for the ocular delivery of therapeutic agents. Applicability of PAMAM dendrimers with carboxyl or hydroxyl end functionalities for ocular delivery of bioactives was found by Vandamme and Brobeck, as this dendrimers increase the retention of pilocarpine within the eyes (Vandamme and Brobeck, 2005).

Yavuz B et al. investigated the ocular absorption of dexamethasone by preparing its conjugate with PAMAM dendrimers. Methyl-thiazol-tetrazolium (MTT) assay revealed that all groups resulted in cell viability comparable to DEX solution. The PAMAM-dexamethasone conjugate showed increased transport of drug across cornea and sclera tissues (Yavuz et al., 2015).

Studies were carried out to evaluate the efficiency of dendrimers as a carrier of bioactives like low molecular weight heparin, enoxaparin for pulmonary delivery. 2G, 2.5G and 3G of PAMAM dendrimers were assessed for pulmonary absorption of enoxaparin in a rodent model. In these studies, it was found that relative bioavailability of enoxaparin was increased by 40% by using cationic charged 2G and 3G dendrimers without any adverse effect on mucocilliary transport rate, and without producing the severe damage to lung tissues. Whereas, negatively charged dendrimers with carboxyl end groups (2.5G) did not influence the bioavailability (Oliveira et al., 2010; Tolia and Choi, 2008).

8.4.4. Stimuli-responsive dendrimer for drug delivery

PAMAM dendrimers have been extensively used for encapsulation and conjugation of drugs and biomacromolecules owing to their internal cavities and multivalent surface groups. The use of PAMAM dendrimers has considerably enriched drug pharmacokinetics and drug targeting. Recent studies are focused on design of stimuli-responsive PAMAM-based nanocarriers possessing potential of controlled drug release, targeted drug delivery and decreased systemic exposure (Zhong and Krishna Rao, 2016).

N-Acetyl-L-cysteine (NAC) is an antioxidant and anti-inflammatory agent and great potential in conditions like stroke and neuro inflammation. Due to high plasma binding after intravenous administration high doses are required which leads to related side effects. Navath et al reported the synthesis and characterization of two conjugates of NAC with a cationic G4-NH_2 and anionic G3.5-COOH PAMA dendrimer. The conjugates showed about 70% of NAC payload within 1 h in response to intracellular GSH concentrations, however negligible NAC release was seen at extracellular GSH levels. The G4-NH_2 and G3.5-COOH conjugates demonstrated higher nitrite inhibition at 24 h and 72 h in comparison to free NAC (Navath et al., 2008).

8.4.5. Carrier for bone targeting

Yamashita et al developed a bone-targeting carrier of PEG-conjugated G3-PAMAM dendrimer for the treatment of bone diseases. Four different types of PAMAM dendrimers were prepared by conjugating the PAMAM backbones to different carboxylic acids viz. aspartic acid, glutamic acid, succinic acid, or aconitic acid. PEG was used to obtain PEGylated carboxylic acid-modified PAMAMs through covalent bonding between PEG and carboxylic acid-modified PAMAM dendrimers. An intra-bone distribution study showed that fluorescein isothiocyanate-labeled PEG (5)-Aspartic acid (Asp)-PAMAM largely accumulated on eroded and quiescent surfaces which is responsible for bone diseases like rheumatoid arthritis and osteoporosis. Thus, the study indicated that PEG (5)-Asp-PAMAM can be used a novel drug carrier for effective drug targeting to the bones (Yamashita et al., 2017).

An overview of the use of dendrimers in delivery of drugs and biological molecules is given in Table 1.

8.5. Dendrimers as diagnostic

The Magnetic Resonance Imaging (MRI) contrast agents conjugated to dendrimer are beneficial due to their tumour-targeting ability. Ye M et al studied a tumour targeting biodegradable dendritic contrast agents (FA-PEG-G2-DTPA-Gd) prepared from a polyester dendrimer conjugated with gadolinium chelates (diethylenetriaminepentaacetic acid – gadolinium (DTPA-Gd) and PEG chains with distal folic acid (FA). The MRI contrast obtained by FA-PEG-G2-DTPA-Gd visualised the inoculated tumour with high clarity and exhibited greater contrast amplification for higher time compared to commercial products, Magnevist. In addition, less retention of Gd was observed in all organs and tissues (Ye et al., 2013).

8.5.1. Photodynamic therapy (PDT)

Dendrimers have been used for delivery of 5-aminolevulinic acid which is a natural precursor of photosensitizer protoporphyrin 1X. The study reports increased accumulation of porphyrin in cells which subsequently resulted in toxicity (Battah et al., 2006; Di Venosa et al., 2006). For enhanced photodynamic effects polymeric micelles with dendrimer phthalocyanine have been investigated as a photosensitizer (Herlambang et al., 2011). More recently, photosensitive drug carriers for PDT having G3 PAMAM grafted porous hollow silica nanoparticles were prepared followed by attachment of gluconic acid to this system. The outer layer which was PAMAM-functionalised having large number of amino groups facilitated higher loading of aluminium phthalocyanine tetrasulfonate. Irradiation of this complete system with light demonstrated effective generation of singlet oxygen which caused significant damage to the tumour cells (Tao et al., 2013).

8.5.2. Dendrimers in boron neutron capture therapy

Boron therapy is based on boron capture reaction for the treatment of cancers (Barth et al., 1992). The PAMAM dendrimers have been explored for the intra-tumour delivery of agents in neutron capture therapy. Wu et al for first time demonstrated the efficacy of a boronated monoclonal antibody for the boron neutron capture therapy of an intracerebral glioma (Barth et al., 2004; Yang et al., 2009). The functionalized G5 PAMAM dendrimers and Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor conjugated to starburst dendrimers carrying about 1100 boron atoms were prepared in this study. In the *in vivo* study, 10 times more accumulation of conjugates in brain tumour tissues was observed as compared to healthy brain tissues.

8.6. Dendrimers as possible globular protein mimics

Due to their high molecular weight and branched architecture they are considered excellent mimics of proteins. Within PAMAM dendrimer family some molecules closely match with the contours and size of many proteins and bio-assemblies. Thus, dendrimers are used in mimicking angiogenesis (Kasai et al., 2002), biomimetic regeneration of hydroxyapatite (Chen et al., 2003), collagen-mimetics (Noriega-Luna et al., 2014; Kinberger et al., 2006).

8.7. Dendrimers in cosmetics industry

Dendrimers are also used in cosmetic industry. L'Oreal holds patent for the product like mascara and nail polish which contains dendrimers. Also it has patent for self-tanning cosmetic composition containing amine dendrimer (Self-tanning cosmetic composition, 2002).

8.8. Enhancement of gene expression

Arima and co-workers synthesized starburst PAA dendrimer conjugates with α-, β-, and γ-cyclodextrins (CDE conjugate) in order to study the improvement in transfection efficiency of nonviral vector. Covalent bonding between α-, β-, and γ-cyclodextrin and dendrimer in 1:1 M ratio was confirmed by 1H NMR spectroscopic study and formation of conjugate between CDE with plasmid DNA (pDNA) was confirmed by agarose gel electrophoretic studies. In a study carried out in NIH3T3 and RAW264.7 cells, it was observed that the dendrimer conjugate with α-CyD (α-CDE conjugate) showed the greatest transfection activity (about 100 times higher) than dendrimer alone and physical mixture of dendrimer and α-CyD. Furthermore, the α-CDE conjugate showed better gene transfer activity than Lipofectin. Thus, from this study it was concluded that α-CDE conjugate can be used as a nonviral vector of choice for pDNA (Arima et al., 2001).

8.9. Antimicrobial activity

It has been established in the literature that the dendrimers exhibit potent antimicrobial activities (without using any antimicrobial agents) after proper surface modifications. The cationic or amphiphilic dendrimers have been investigated for antimicrobial activities against a variety of pathogens. The electrostatic interactions between the membrane of pathogens and dendrimers causing membrane disruption and cytoplasm leakage has been proposed as a primarily mechanism of antimicrobial activity of dendrimers (Hao-Jui and Jason, 2017; Worley et al., 2014).

But, cationic dendrimers also causes membrane disruption on mammalian cells thus the selectivity of dendrimers for microbial membrane is a key concern. Researchers demonstrated the nitric oxide (NO)-releasing PPI dendrimers to address this problem associated with cationic dendrimers (Worley et al., 2014; Lazniewska et al., 2012; Sun et al., 2012; Lu et al., 2013).

Due to synergistic antibacterial activities of NO and cationic dendrimers, it is possible to decrease the concentration of cationic dendrimers which consequently increases biocompatibility with mammalian cells.

Sun B and co-workers developed NO releasing PPI G2 and G5 dendrimers. The highest biocide activity (> 99.99% killing) was seen against both Gram-positive and -negative bacterial strains including the antibiotic-resistant and methicillin-resistant *Staphylococcus aureus* (MRSA) strain. Furthermore, minimal toxicity was observed to the fibroblasts. The beneficial effects of dendrimer-based antiviral agents have also been established by the researchers. Briefly, antiviral dendrimers primarily inhibit the virus from binding to the host cell surface by blocking the binding sites via multivalent binding (Sun et al., 2012). In a study carried out by Landers JJ et al it was observed that sialic acid functionalized PAMAM dendrimers entirely preclude mice from being infected by murine influenza pneumonitis (Landers et al., 2002).

Garcia-Gallego et al studied the metal complexes of carboxylated and sulfated PPI dendrimers where inhibition of HIV-1 infection was noticed via inhibiting the internalization of HIV-1 into epithelial cells (Garcia-Gallego et al., 2015).

9. Conclusions

Dendrimer have the properties of high degree of branching, multivalency, globular architecture and well defined molecular weight. Several types of dendrimers are present based on their structural characteristics thereby offering new scaffolds for drug delivery. Drugs can be efficiently incorporated into the dendrimer by several interactions due to its promising structure. Multistep synthesis gives low yield which can be overcome by click chemistry method, thereby making it convenient to synthesize them. Physicochemical properties make them a promising class that helps in improving solubility, bioavailability, permeability and diagnostic applications. Although the toxicity due to them exists, but it can be managed by certain modifications into the structure. The overall benefits presented by the dendrimer nano-architectures have fascinated remarkable attention by researchers not only in drug delivery, but also in the diagnosis and management of disease. The use of dendrimers in diagnosis of disease particularly cancer, is very significant since the early detection increases the chance of its successful treatment. The application of dendrimers for the transfection of siRNA/other genes, *in vivo* gene-delivery studies, and carrier for gene–drug combination directly to the target site is very exciting. Thus, Dendrimers hold a promising future in drug delivery and biomedicine.

Conflict of interest

The authors have no conflict interest in publication of this manuscript.

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