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A Comprehensive review on Dendrimers in current advanced Drug delivery

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Abstract

In this particular review, it is been noted that Dendrimers are novel three-dimensional globular nano-polymeric structure; having multiple functional groups on the surface enhances their function. Synonymous terms for dendrimer include arborols and cascade molecules. The importance of dendrimers in a large variety of fields has been detected, where the various types of dendrimers helps in various fields of drug delivery with the different types of dendrimers with the generation. Hence the dendrimer gains more attention from researchers among various nano-materials. Convenient synthesis of the structure makes them as a good nano-material for drug delivery. In recent, dendrimers showed their activity in different drug delivery systems having properties like cancer targeting, anti-bacterial, ocular drug delivery, etc.. The future direction about the dendrimers are been discussed. The present review is focused on types of dendrimers like Polypropylene Imine dendrimer (PPI), Poly(amidoamine) dendrimers (PAMAM), Poly-l-lysine dendrimers, Type of Frechet's dendrimer, Core-shell tecto dendrimers, Chiral dendrimers, Liquid crystalline dendrimers, Peptide dendrimers, Multiple antigen peptide dendrimers, Glyco-dendrimers, Hybrid dendrimers, Polyester dendrimers in which among these type of dendrimers, the Polypropylene Imine dendrimer (PPI) and Poly(amidoamine) dendrimers are found to be good carriers for various targeting site, Dendrimers are synthesized through various methods like Divergent method, Convergent method, Hyper cores and branched monomer growth method, Double exponential growth method, Click chemistry method, recent advances in dendrimers are used in the Anti-cancer delivery, Anti-bacterial delivery, oral route delivery, pulmonary drug delivery, transdermal drug delivery, ocular delivery, and targeted drug delivery the safety aspects, and future strategies are also been discussed in the below article.

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INTRODUCTION

Dendrimers are nano-molecule, tree-like branched structures, which are having radially symmetric molecules (Campbell *et al.*, 2007). Dendrimers are known as single disperse macromolecules, which are having symmetric branching units around a core. These nano-molecules were first exposed by Fritz Vogtle in 1978. Arborols are called as a second group of the synthesized macromolecules. Cascade molecule is another name of the dendrimer, but the cascade term is not used as much as the den-

drimer term (Newkome, 1985; Tomalia, 1985). Size, shape, and flexibility of the dendrimers changes as the generation increases. Hence the dendrimer molecule is known as architectural design but not a compound (Gennes and Hervet, 1983; Mansfield and Klushin, 1993). Dendrimers are hyperbranched macromolecules with a carefully tailored architecture, which can be functionalized and modify their physicochemical or biological properties (Bosman *et al.*, 1999; Gillies and Fréchet, 2005).

The structure of the dendrimer has three phases,

1. An atom or a molecule is present at the center of the structure, which is called as a core having some chemical functions.

2. Branches are then ejected from the core and adds on repetitively having one junction of a branch, as the repetition is carried further, will results in a radial concentric layer called "generations."

3. Terminal groups are usually situated on the surface of the dendritic structure. These surface groups are used to identify the properties of the dendrimer (Frechet, 1994).

To observe different functions of dendrimers, various types of dendrimers are given below. Different types of dendrimers are synthesized by different methods. Usually, the synthesis of the dendrimer is from a central poly-functional unit called as a core, by the recurring attachment of monomers. On the other hand, the various functional groups are added on to the core. Monomer additions with all functional groups will fallout to the next generation of a dendrimer, along with the appearance of the last group for additional reactions. In which synthesis includes divergent method, convergent method, hyper cores, and branched monomer growth, double exponential growth, and click chemistry (Stockigt *et al.*, 1996; Klajnert and Bryszewska, 2002).

Advancements to happen in the dendrimer for the delivery of drugs have taken tremendous interest among the scientists. Hence in this review, we provide about various distinctive types of dendrimers described in Figure 1 with different properties, synthesis of dendrimer through various reactions, mainly advancements happened by the dendrimer for the delivery of a drug is given below and safety aspects of the dendrimers (Kesharwani *et al.*, 2014c). Overall, Dendrimers have good features, which makes them a good candidate for many conditions.

MATERIALS AND METHODS

Types of Dendrimers

Few of the dendrimers having a variety of functions are described in Table 1 , (Kesharwani *et al.*, 2014a).

Polypropylene Imine dendrimer (PPI)

PPI dendrimers is the oldest one, and it was invented relating to the propylamine moieties (Sherje, 2018). It is synthesized by the Divergent method and Michael addition reaction method (Mendes *et al.*, 2017; Gupta *et al.*, 2018). 1, 4-diaminobutane acts as a core in the preparation of poly(propylene imine) Dendrimers. During the synthesis of PPI dendrimer 1, 4-diaminobutane is utilized as a dendrimer core. Various molecules, along with the primary or secondary group of amines, can also be utilized as core in the preparation of PPI (Den *et al.*, 1993). Branching units consisting of alkyl chains leads to the hydrophobic personality of PPI Dendrimers. When compared with PAMAM Polypropylene, Imine contains a greater core (Cheng, 2011).

Poly (amidoamine) dendrimers (PAMAM)

PAMAM dendrimers are used in target-specific delivery of chemotherapeutical agents, peptides, and many chemicals. It is a commonly used carrier for many drugs due to its potential. Various surface modification have made PAMAM dendritic structure a hopefull nanocarrier in the treatment of cancer. PAMAM dendrimers plays a main role in light-harvesting devices and also used as a vaccine adjuvant. (Delivery, no date) Surface modified dendrimers consisting of ligand, helps in biological targets. However, commercially assessable polyamidoamine and polypropylene imine are promisingly considered for usage in biomedics (Duncan and Izzo, 2005). These dendrimers are mainly synthesized from a divergent method (Sharma, 2017).

When compared to other dendritic structures, the particle size distribution of PAMAM is uniform in all the generations, because the polydispersity index is between 5.0G to 10.0G is below 1.08. The compression of DNA and transfection can happen from the PAMAM dendrimers because of the positive charge present on the surface of the molecule (Kesharwani *et al.*, 2014a).

Poly-l-lysine dendrimers

Poly-l-lysine dendrimers are biodegradable carriers used for the delivery of solid tumor-targeted cytotoxic drugs (Kaminskas, 2011). Poly-l-lysine are peptide dendrimers having more compactness with the oligonucleotides, so it is used to carry genetic materials (Wu *et al.*, 2013). Due to its asymmetric structure, it differs from PPI and PAMAM

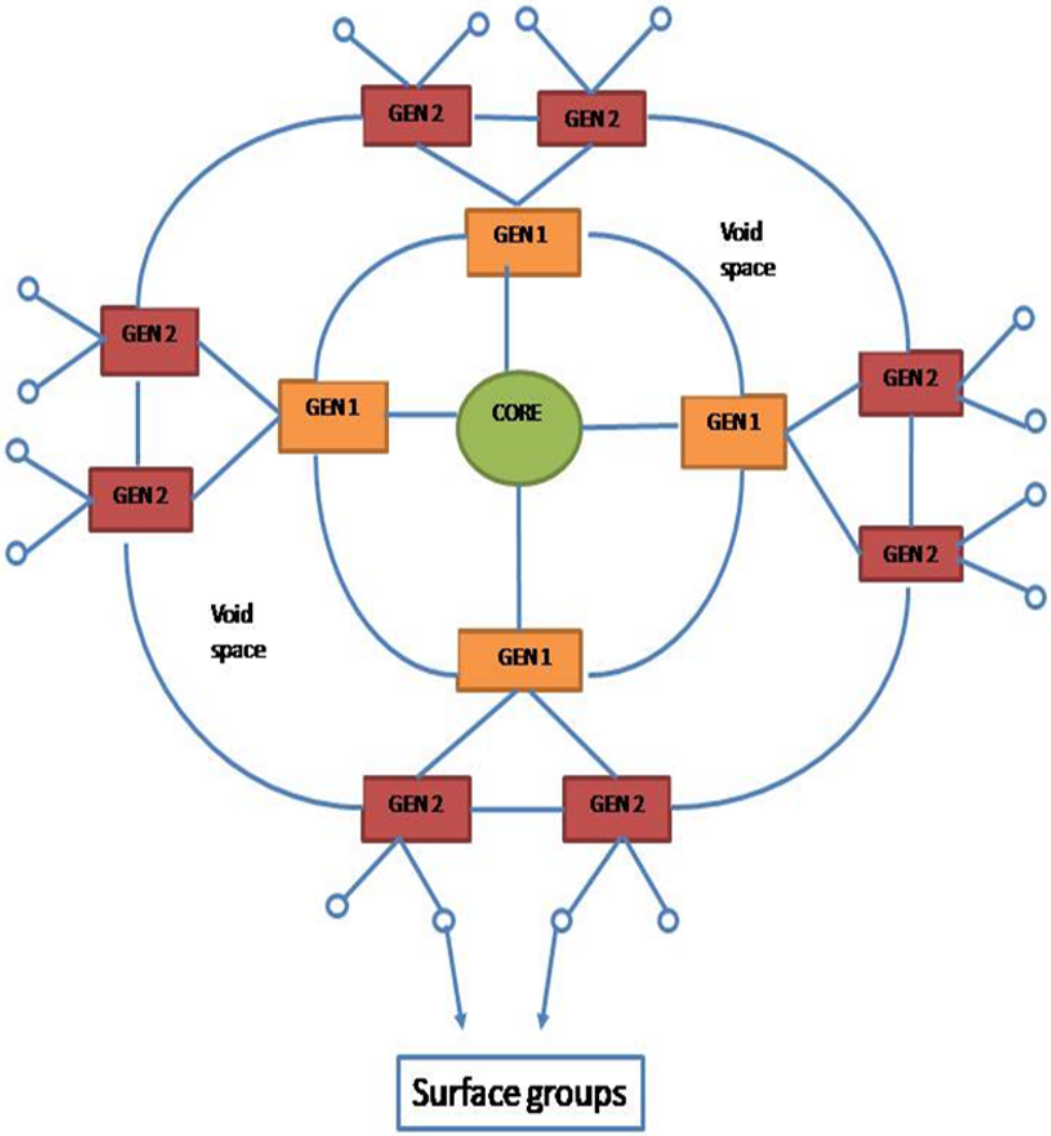

Figure 1: Schematic representation of dendrimer (Gen = Generation)

Table 1: Theoretical details of different generations of PAMAM and PPI dendrimers

Dendrimer type	Poly(amidoamine)			Polypropylene Imine		
Generation	Surface groups	Molecular formula	Molecular weight	Surface groups	Molecular formula	Molecular weight
0	4	C22H48N10O4	517	4	C14H36N6	288
1	8	C62H128N26O12	1430	8	C38H92N14	746
2	16	C142H288N58O60	3256	16	C86H204N30	1658
3	32	C302H608N122O88	6909	32	C182H428N62	3486
4	64	C622H1248N250O124	14215	34	C374H876N126	7146
5	128	C1282H2528N508O252	28826	128	C758H1772N254	14436

dendrimers. Hence, their structural arrangement is perfect with terminal amine residues and with a controlled amount of lysines branching with a core (Mendes *et al.*, 2017). This dendrimer is more beneficial because it possesses anti-angionic property, stimulating apoptosis and demolishing of necrosis, which helps in the tumor microenvironment (Kostarelos, 2010; Jain and Jain, 2014).

Type of Frechet's dendrimer

These dendrimers were freshly recognized by the Hawker and Frechet (Hawker and Fréchet, 1990; Cao *et al.*, 2002; Hawker *et al.*, 2004). This dendrimer consists of the hyper-branched structural design of poly-benzyl ether. Modulation of functional group in a terminal of the branch occurs due to the presence of the Carboxylic group (-COOH) as the terminal group and rewarding better branching points. Additionally, in this dendrimers, the solubility in aqueous media and polar solvents increases when the polar terminal groups are present (Abbasi *et al.*, 2014).

Core-shell tecto dendrimers

Tecto dendrimer is a composite dendrimer where the dendritic structure itself behaves like a core, and these dendritic structures are covered by various other dendrimers (Gupta and Perumal, 2014). The available four various types of tecto dendrimers are differentiated by tapping mode atomic force microscopy. PAMAM dendrimers are known as the base of Tecto dendrimers, which consists of G-4G-3, G-5G-3, G-6G-4, and G-7G-5 (Li, 1999).

Chiral dendrimers

The improvement of the dendritic structure has seen the realization of a different range of architecturally attractive macromolecules that have created notice in the recent literatures. Possibly the most synthetically competitive hyperbranched polymeric structures are chiral dendrimers (Romagnoli and Hayes, 2002). The dendrimers having chiral or non-racemic structure as a subclass with good defined stereochemistry are helpful in applications, like chiral recognition and asymmetric catalysis (Ritzén and Frejd, 1998). In the internal and periphery of the carbohydrate unit and 1,3,5- trisubstituted aromatic core, which contains the first molecules of anthracene covered chiral dendrimers, which was described by Ghorai *et al.* (2004). These functions of chiral dendrimers are helpful in the novel drug delivery system and also used for the light-harvesting materials (Ghorai *et al.*, 2004).

Liquid crystalline dendrimers

From the past few years, the interest towards the liquid crystalline dendrimers have been gradually increasing (Donnio, 2007). The addition of the mesogenic group into the hyperbranched dendritic scaffold can get Liquid crystalline dendrimers (LCDs). The addition can be done by two methods,

1. Random self-polymerization of a suitable bifunctional mesogenic monomer (Park *et al.*, 2002).
2. Grafting of mono functionalized mesogenic units at the terminal branches of the polymer (Donnio, 2007).

The problem of the 5^{th} generation of the Liquid crystalline dendrimer is been short of mesomorphism because it fails to be recognized as cylindrical in shape. LC Dendrimer, which consists of a terminal group with cinnamoyl groups which acts as photosensitive, is very much helpful in recent drug development (Boiko, 2001).

Peptide dendrimers

Nowadays, the mission for good gene delivery issues is the main factor for the victorious therapy of genes. Peptide dendrimers are well-known candidates for their efficiency in non-viral gene delivery vectors (Luo, 2012). In recent times, the requirement of peptide dendrimers in gene delivery is high in level, due to its flexibility, amino groups in an external surface, good biocompatibility, and conflict to proteolytic digestion (Luo, 2011).

Multiple antigen peptide dendrimers

MAP-Multiple antigen peptide dendrimers have around two or three structural arrangements like branching units and functional groups on the surface. Fascinatingly, this dendritic structure consists of both α-peptide and ε-peptide. These structures can also be synthesized without a core. Hence it is called as 'dendrons' and not often called as dendrimers. Though, for the purpose of study, poly-peptide structures are considered as dendrimers (Sadler and Tam, 2002).

Glyco-dendrimers

The Glyco-dendrimers are a very important class of dendrimers. It has a great capability as a drug carrier. There are several divisions of this dendrimer, which mainly includes carbohydrates in its structure. Furthermore, glycodendrimers have saccharide residues on the outer surface of their structure. It also contains a sugar unit as a core, and all other branches are developed around the core (Oliveira, 2010).

Hybrid dendrimers

This dendrimer is a mixture of dendritic polymers and linear polymer, which are appeared as in the

form of fixed co-polymer or hybrid block. These dendritic structural hybrids are compressed, strong, and uniformly branched molecular structure. This dendrimer acts as a good carrier for many of the drug delivery system. This dendrimers are formed due to the spherical structure and more amount of terminal groups (Louvain *et al.*, 2010; Kesharwani *et al.*, 2014a).

Polyester dendrimers

These dendrimers have been widely studied by the Scientists starting from the core to the branches and terminal groups. Polyester dendrimers are not complex in preparation, and whenever the evaluation is done on this dendrimer, usually, the result was non-toxic. Hence, this dendrimer has more importance in several drug deliveries. Recently, the polyester dendrimers have got a newer approach for synthesis called bi-functional orthogonally reacting dendritic structure, and a positive result is seen in this synthesis. The main step involved in the synthesis is the formation of the ester bond in the dendrimer synthesis (Twibanire and Grindley, 2012).

Synthesis of Dendrimers

Dendrimers can mainly synthesize by two methods; one is by molecular chemistry, where the dendritic molecules are prepared by the stepwise controlled method. The second one is by polymer method, repetitive branching from the core, which is made of monomers (Abbasi *et al.*, 2014).

Synthesis by Divergent method

Divergent methods of synthesis were used in the early days. The arms are attached to the core in a stepwise manner, like building blocks (Abbasi *et al.*, 2014). Dendrimers which are synthesized by the divergent method are very useful to modify their surface molecules by altering the end group at the last generation, and these dendrimers also have the capability of configuring the need of chemical and physical properties (Ong, 2001; Islam *et al.*, 2005).

Furthermore, Divergent method of synthesis consists of two main disadvantages,

Firstly, as the reaction point increases very fast, simultaneously, molecular weight also increases. This process slowdowns the reaction kinetics and make problems in the synthesis of the higher generation. As a result, an increase in molecular weight increases deletions in the synthesis of dendrimers, which causes various problems in the higher generation of the molecule.

Secondly, as the deletion or differentiation of the required products from the reactants becomes difficult to major molecular familiarity in between of required and byproducts.

Apart from all problems, the divergent method of synthesis is still used for the preparation of dendrimers (Boas *et al.*, 2006).

Synthesis by Convergent method

The convergent method of synthesis is opposite to divergent synthesis. Firstly, the dendrons are prepared from the periphery, and it is attached to the core in the final step will make a dendrimer. Even though this synthesis have many advantages over the divergent process, this synthesis becomes very complex due to the generation's slow process of reaction (Vandendriessche, 2009). Usually, Poly (aryl ether) is the skeleton for the dendritic structure, which is synthesized by the convergent method (Pandita, 2014).

Hyper cores and branched monomer growth in dendrimer synthesis

To obtain better results in this type of synthesis is by the arrangement of oligomer moieties, which are then attached with each other to obtain a dendrimer (Nanjwade, 2009). A core with surface units develops the hyper core, which consists of multiple attaching groups are connected with branched monomer, along with a synthesis of blocks by focal point establishment, which are then linked with a hyper core to synthesize a higher generation of dendrimers.

Synthesis of dendrimers by Double exponential growth

These are the linear polymers which consist of fast growth technique. In this synthesis, the starting material is the same monomer for divergent and convergent growth. Then the 2 products interact with each other to give orthogonally secured timer. Repeated growth of timer produces a dendrimer. Due to the rapid growth, divergent and convergent coupling can be done (Juris, 2003).

Click chemistry

Click chemistry is one of the most important and leading reactions when compared with other reactions. To build higher generations of dendrimers, finished or 95 percent of the exchange of chemistry is not enough. It is very complicated to maintain purity in the stepwise process, and therefore monodispersity of a dendrimer is observed. Convergent and divergent method of synthesis needs the study requirements for orthogonality. There are a few reactions which gives results over 99 percent and better orthogonality with each other (Arseneault *et al.*, 2015). Due to this reason, click chemistry has become a promising factor for many dendritic structures. Application of click chemistry in

material chemistry also shown good results and reviewed in more numbers, and this is beyond dendrimers (Such, 2012; Xi, 2014).

Current Advancement in Dendrimer Drug Delivery

Anticancer delivery

In the current situation, there are various problems for anti-cancer targeting therapy, and also to develop a unique carrier system is again a dispute mentioned in the Figure 2 , (Dande *et al.*, 2006). Dendrimers are macromolecular nanosized 3-dimensional structures, consists of a middle core and a hyperbranched structure around and a corona with a functional group, and dendrimers are unique in structure (Tomalia, 2005). Dendrimers are easily prepared by the convergent and divergent method of synthesis. (Ihre *et al.*, 2003). Each and every steps are regulated over the preparation of dendritic structure will helps the dendrimer as a good nanocarrier with assumable properties for anti-cancer therapy. Various types of dendrimers, including polyamidoamine (PAMAM), polypropyleneimine (PPI), poly-l-lysine (PLL), melamine, and triazine are good nanocarriers for anti-cancer therapy. Furthermore, citric acid-based and carbohydrate-based dendrimers has shown good results in targeting for cancer (Liu and Fréchet, 1999; Patri *et al.*, 2005; Crampton and Simanek, 2006; Kesharwani and Iyer, 2015; Tomalia *et al.*, 2016).

Amongst others, the most important, the more required, and rapidly used are PAMAM and PPI-based dendrimers (Kannan *et al.*, 2009; Kesharwani *et al.*, 2014a,b). Significantly, PAMAM ad PPI dendritic structures having an amine group on the terminal position shows the stimuli-responsive or pH-dependent drug release performance. In fact, when the amine-terminated dendrimer is exposed to high pH, then the tertiary amino group present on the structure gets de-protonated, leading for the fall down of the dendritic structure on itself, which is called as 'back folding.' Under these situations, the cascade molecules can easily grab more of drug molecules within the cores, ensuing of compaction of dendritic structure. On the other hand, dendrimer which is exposed to the lower pH, causing a tertiary amino group to protonate and leading charges to repulse. Clear swelling and 'extended conformation' will leads to sustained and prolonged release of an entrapped drugs due to repulsion of the charges. However, the tumor surrounding will be slightly acidic, so to treat the cancer cells for the long-term, these dendrimers, which are capable of releasing the drug for a prolonged time, can be used. ('Formulation development and in vitro – in vivo assessment of the fourth-generation PPI dendrimer as a cancer-targeting vector,' 2014)

Anti-bacterial delivery

Dendrimers have the capability of increasing the local concentration for the functional group. If the dendrimers are added with the active substance can assume the increase in efficiency with increased local concentration; though, the dendrimers used for anti-microbial must be selected consciously. As the molecular weight of the dendrimer increases, it cannot pass through the cell membrane and complicate it to serve the drug to the target site. Usually, biocides added on to the dendritic structure will become more potential if the target is cell membrane. While it is promising to incorporate antimicrobial groups on the dendrimers and increase their potency, an alternative way is to design dendrimer-based drug delivery systems. Here two sets of examples are described. The principle of the first set is to design novel drug delivery systems based on the single molecular micellar structure of dendrimers. The second example is hard to classify since these structures and the mechanisms of antimicrobial properties are not fully understood. They share some characteristics of both the incorporation of antimicrobial groups and drug delivery systems (Chris *et al.*, 2000).

Dendrimers used in oral route delivery

The oral route of administration of the drug has become the good route for its many advantages. This route is mostly used by the patient because it is easy to administer as per the patient compliances. Among all the merits, it also has some demerits like low solubility in aqueous media and less diffusion through the GIT track. D'Emanuele and his team (Kesharwani *et al.*, 2017) invented the effect of dendrimer generation and conjugation on the cytotoxicity, diffusion, and transport mechanism of PAMAM dendrimer. As the concentration or generation enhances, the cytotoxicity also gets increased and diffusion as well. If lauryl chloride is conjugated, then the cytotoxicity decreases. Surface modification of dendrimer also reduces the trans-epithelial electrical resistance (TEER) and prominently increased the permeability coefficient. Hence, this type of conjugation helps in the bio-availability increase in oral delivery (Emanuele, 2004).

Dendrimers in pulmonary drug delivery

Dendrimers are very good nano-carrier for pulmonary diseases. In one of the studies, the PAMAM dendrimers were used to treat the pulmonary dis-

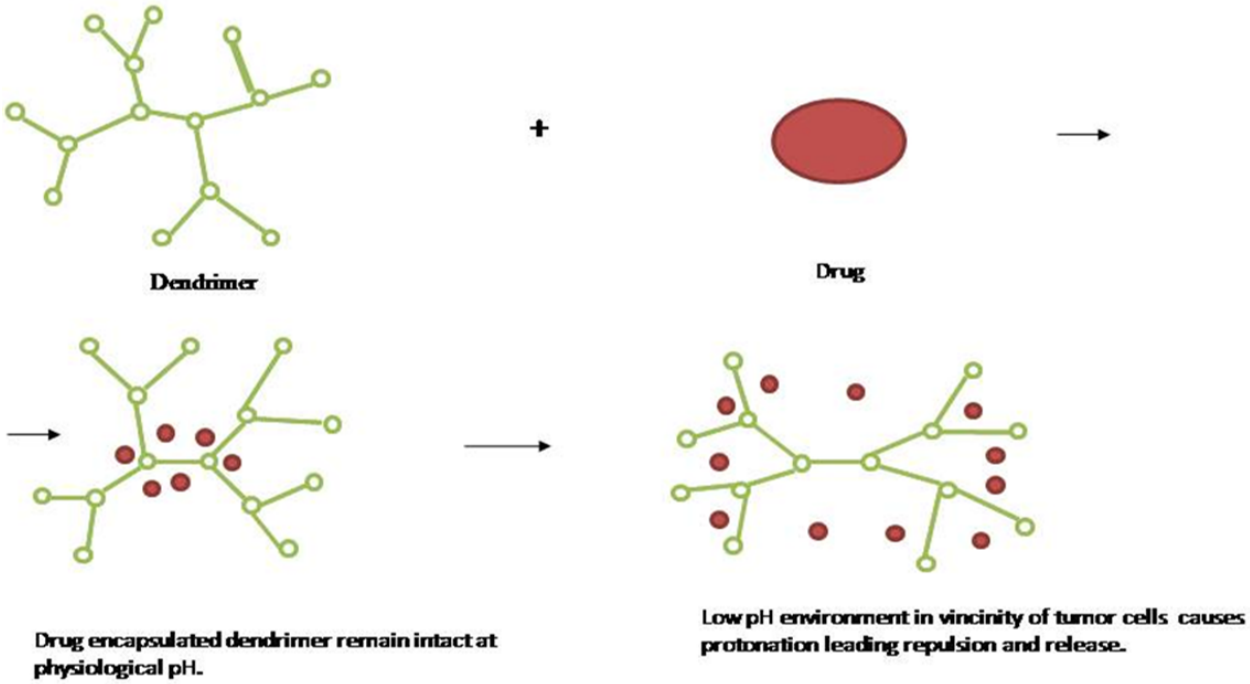

Figure 2: Anti-cancer mechanism of pH-dependent drug-releasing through the dendritic structure

ease and came to know that it has to enhance pulmonary permeation of Enoxaparin by checking the plasma anti-factor behavior and also studied for the inhibition of potential of deep vein thrombosis by a Rodent replica. The positive make-up of the PAMAM dendrimer of G-two and G-three generations enhance the bioavailability of Enoxaparin with 40percent, but the G-2.5 PAMAM, incomplete generations of dendrimers with negative make-up with the carboxylic group, shows zero effect. By comparing both positive make-up and negative make-up, the positively charged dendrimers are good, a potential nano-carrier system for Enoxaparin pulmonary delivery (Bai *et al.*, 2007).

Dendrimers in transdermal drug delivery

In recent years, dendrimers have taken a good initiative for transdermal drug delivery.

Reasons of dendrimer used in transdermal delivery

1. The inhibition of entry of a drug into the biological compartments is due to hydrophobic moieties present in the drug, which results in reduced water solubility.

2. High water-soluble and biocompatibility of premediated dendrimers.

The pharmacokinetic parameters of the dendrimer are suggested as a good nano-carrier for the transdermal delivery of the drug. Dendrimers are also tested with a variety of non-steroidal anti-inflammatory drugs for to deliver in the transdermal area (Nanjwade, 2009).To deliver in the transdermal site by using dendrimer as a carrier with the non-steroidal anti-inflammatory drugs is also tested. By using indomethacin as a drug with 4.0G of PAMAM dendrimer with hydroxyl terminal and amino and 4.5G PAMAM dendrimer is used for transdermal delivery, this experiment was carried out by Jain and coworkers. When PAMAM dendrimer with indomethacin was studied on Wistar rats (in vivo) and checked for the pharmacokinetic and pharmacodynamic parameters and resulted with the increase in the concentration of drugs in the blood (Chauhan, 2003). Soon after, the conjugation of ketoprofen and di-flunisal with 5^{th}G of PAMAM dendrimer was developed by Cheng and coworkers. While performing the in vitro diffusion studies with Wistar rat skin, ketoprofen and diflunisal along with dendrimer showed 3.2- and 3.4-times greater permeation when compared with to the ketoprofen and diflunisal in the saline solution. However, the authors stated that NSAIDs delivered along with dendrimers are having a good therapeutic result and also helps in increasing permeation, which really helps in transdermal delivery.

Dendrimers in ocular delivery

The main drawback of the ocular delivery is poor bioavailability, while the medication is applied through topical by bioactive. The two main problems associated with removal of the formulation are,

1. Nasolacrimal duct treats excess fluid as drainage

2. Elimination by tears

Due to overcome these problems, new formulations are in interest. When it comes to the ocular delivery, the formulation must be isotonic, non-irritating, non- sensitizing, biodegradable, and biocompatible with prolongation of formulation in the region of the eye. However, dendrimers has taken nice initiatives to deliver in the ocular region with good retention time. By using pilocarpine with PAMAM dendrimer consisting of carboxyl or hydroxyl as terminal functionalities, enhances the retention time in the region of the eye, this was proposed by Vandamme and Brobeck. Hence, this study states the importance of dendrimers in the ocular delivery of drugs (Nanjwade, 2009; Jain, 2012).

Dendrimers in targeted drug delivery

In recent times, drugs which are released to the target site have more efficacies when compared to other deliveries. This type of delivery system decreases the side effects and enhances the therapeutic index of the drug. A dendritic structure can easily provide the targeting of a drug by a passive or active process, so this process helps in the treatment of cancer, which is caused by the parasitic infection, which can be achieved by surface modification of engineering of structures. The main advantage of target delivery is that the target site will be well defined so that the suitable dendritic structure can be developed. Dendrimers has great properties to deliver for the targeted site due to its surface groups, monodispersed, and architecture. Hence these properties make a dendrimer as a good carrier medium for the delivery of drugs. The best example for anti-cancer targeting of tumor drugs is by folate conjugated dendrimer. Since the breast cancer cells (ovarian cells) has more number of folate receptors, it helps the folate conjugated dendrimer to efficiently target with anticancer drugs (Quintana, 2002; Agarwal, 2008). A study was carried out on folate conjugated with PAMAM dendrimer containing methotrexate (MTX) as a drug and studied on an immune deficiency of mice and collected the biodistribution data.

Bio-distribution data of folic acid conjugated with dendrimer shows increased accumulation in cancer cell after 24 hours when compared with those not conjugated with folic acid. The good surface modification or engineering of structure can provide multifunctional as a target medium. Jain and co-workers invented bi-ligand conjugated PPI dendrimers for a dual approach towards anti-HIV by using zidovudine as a drug. Hence the dual conjugation helps in enhancing the compatibility and targeting capacity of antiviral drugs (Gajbhiye, 2013).

RESULTS AND DISCUSSION

Safety Aspects of Dendrimers

Dendrimers which are having positive surface groups will have more affinity to interact with the cell membrane; hence, the absorption becomes an easy process. The interaction between the cationic surface of the dendrimer and the cell membrane may also lead to malfunction and cell lysis by leaking of cytosolic proteins (Rittner *et al.*, 2002; Chen *et al.*, 2004; Mecke *et al.*, 2005). As the concentration and generation of the PAMAM dendrimer enhances, cytotoxicity also increases in parallel and may lead to hemolysis, and it may also happen due to the cationic charged amino group on the surface of the PAMAM. So, this holds-on the efficiency in pharmaceutical and biomedical problems (Klajnert *et al.*, 2004; Kukowska-Latallo, 2005; Kesharwani *et al.*, 2014a).

Dendrimers containing cationic groups on the surface will causes hemolytic toxicity and cytotoxicity. But their toxicity can be abolished by surface modification with ligands, which are biocompatible such as peptides, amino acids, acetyl group, carbohydrates, and PEG. Hence the surface-modified dendrimers results in biocompatible and helps in reducing toxicity (Jain *et al.*, 2010; Jain, 2012).

In another study, the scientist has determined that the anionic surface of the dendrimer is less cytotoxic compared with the cationic surface dendrimer of the PAMAM. The anionic or the half-generation dendrimers with Caco2 cells shows less cytotoxicity.

There are two main methods for abolishing the in-vitro toxicity issues of dendritic structure,

1. We can formally put an end to in-vitro toxicity by preparation of biodegradable dendrimers like polyether, melamine, peptide, and polyetherimides dendrimers.

2. We can cover the cationic charged surface dendrimer by acetylation or PEGylation (Jain *et al.*, 2010).

Future Stratergies

Among all the dendrimers, biocompatible dendrimers are more tend to use as a carrier and has a better class of nano-materials. These biodegradable dendrimers have to main merits over other conventional dendrimers, and the merits of biodegradable

Table 2: Merits of biodegradable dendrimer

Serial No	Merits
01	The bioactive substance is released from the dendrimer by a single cleaving reaction only when the bioactive substance consists of many covalent bonds.
02	It readily eliminates from the body without any gathering into the cells/tissues. Therefore biodegradable dendrimers are more used.

dendrimers are been discussed in the Table 2 (Leiro *et al.*, 2015).

Biodegradable dendrimers also have some problems in solubility when it attached with some functional groups and bio-molecules.

In reality, the results in early years shows that the biodegradable dendrimers are suitable for only a few particular functions and more studies or review is done only for the design and preparation or synthesis of biodegradable dendrimers. As per the above, further surface modifications should be done for the better activity of the dendrimers. However, the dendrimer overcomes the problem, and then biodegradable dendrimer is required to retain its therapeutic activity. The various mixture of biodegradability and multivalence makes a dendrimer as a good platform for the delivery of the drug and flexible for various biomedical importance revised here (Leiro *et al.*, 2015).

CONCLUSIONS

Dendrimer have the properties of a high degree of branching, multivalence, globular architecture, and well defined molecular weight. Several types of dendrimers are presently 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. Even though the toxicity exists in them, 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 a disease. The use of dendrimers in the diagnosis of disease, particularly cancer, is very significant since early detection increases the chance of its successful treatment. Dendrimers can mainly synthesize by two methods; one is by molecular chemistry, where the dendritic molecules are prepared by the stepwise controlled method. The second one is by polymer method, repetitive branching from the core, which is made of monomers When it comes to recent advancements of a dendrimer. It has versatile advantages towards anti-cancer. In ocular delivery, dendrimer helps the drug to retention time in the region of the eye. Folate conjugated dendrimer along with the drug will helps in targeting to gene delivery. The various mixture of biodegradability and multivalence makes a dendrimer as a good platform for the delivery of the drug and flexible for various biomedical importance. In this review, types of dendrimers, synthesis of a dendrimer, current advancements in dendrimers, safety aspects, and future strategies of dendrimers has been reviewed.

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