Strategies in Dendritic architecture for drug delivery – An over review

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ABSTRACT

Dendrimers represent a novel class of structurally controlled macromolecules derived from a braches upon branches structural motif. These consist of highly branched moieties that radiate from a central core and synthesizes through a stepwise repetitive reaction sequence. In the field of pharmaceutical nanotechnology and medicinal chemistry dendrimers play a vital role based on the structural advantage such as size, shape, surface and interior chemistry flexibility and topology. Dendrimers have emerged as highly gifted drug delivery molecule because of their exceptional structure and properties. Solubility enhancement is an important aspect of dendrimers and this is a synergy with site specific drug delivery. Solubilisations of hydrophobic drug molecule are easily achieved by the dendrimers because they were entrapped in hydrophobic channels. Extracellular matrix of tissue particularly vascular tissue it contains a high concentration of negatively charged glycosaminoglycans which are involved in regulation of cell motility cell proliferation in the regulation of enzyme activity. Extra cellular matrix can be used as a substrate for binding and retention of drug delivered intra vascularly. Recently dendrimers have caused an explosion in biomedical science and created interest in the discovery of the drugs by virtue of their therapeutic value. The dendrimer polymer suggest that they are promising drugs wound healing ,bone mineralization cartilage formation, tissue repairing topical treatment for AIDS to prevent HIV transmission. It also acts as an anti prion, anti Alzheimer, anti coagulants, anti dots, anti inflammatory and anti cancer agents.

Key Words: Dendrimer, Nano-composites, Dendrimer conjugation, Dendrimer applications.

INTRODUCTION

Dendrimer the name comes from the Greek "δενδρον"/dendron meaning "tree" synonymous terms are arborols and cascade molecule (Buhleirier *et al*., 1978). Dendrimers are repeatedly branched molecules that are characterized by structural perfection. This is based on the evolution of both symmetry and polydispersity the field of dendritic molecule can roughly be divided into

1. Low molecular weight
2. Molecular weight species

The first category includes dendrimers and dendrons and the second includes dendronized polymers hyper branched polymers and brush polymers (called as bottle brushes) tailored forms and function ever realized outside of nature. Structurally dendrimers posses 3 distinct parts

1. A core
2. Branching units
3. Branches

It is usually produced in an interactive sequence of reaction steps, in each added lerative lead to a higher generation material. The size of dendrimer can be described as a function of generation (Gn where n is 0, 0.5, 1.0, and 1.5) G is number of repetition cycles. The molecular weight of the dendrimer nearly doubles with each additional generation (Tomalia *et al*., 2005). Furthermore, terminal groups can be modified to obtain both hydrophilic or lipophilic function for the desired biological and drug delivery application (Bai *et al*., 2006). Following properties of dendrimer made them ideal molecule for drug delivery applications (Tomalia *et al*., 2007):

a. Nanoscale sizes that have similar dimensions to significant bio-building blocks,
b. Numbers of terminal surface groups (Z) appropriate for bioconjugation of drugs, signalling groups, targeting moieties or biocompatibility groups.
c. Functional groups on the surfaces were designed to augment or resist trans-cellular, epithelial cell or vascular permeability.
d. An interior void space was used to encapsulate drug molecule, metals, or imaging moieties and also reduces the drug toxicity and facilitates controlled release.
e. Positive biocompatibility patterns that are coupled with lower generation anionic or neutral polar terminal surface groups.
f. Low-immunogenicity with modified dendrimer surfaces by small functional groups or polyethylene glycol (PEG).

Dendrimers a nano particle based drug delivery system have numerous applications in many fields such as supramolecular chemistry or host–guest chemistry (Elemans *et al*., 2002 and Al-Jamal *et al*., 2005), electrochemistry (Credi *et al*.,

2004), and photochemistry (Momotake *et al*., 2004), nanoparticle synthesis (Wu *et al*., 2006, Love *et al*., 2006 and Yan *et al*., 2006), pollution management (Xu *et al*., 2005, Diallo *et al*., 2005 and Arkas *et al*., 2006), dye decolorization (Cheng *et al*., 2005 and Cheng *et al*., 2005), preparation of monomolecular membranes (Karthaus *et al*., 1996, Sayed-Sweet *et al*., 1997 and Vladimir, 1998), curing of epoxy resins (Cheng *et al*., 2007), catalysis (Lee *et al*., 1994, Fujita *et al*., 1995, Bhyrappa *et al*., 1996 and Mak *et al*., 19970, drug delivery (Patri *et al*., 2002, Aulenta *et al*., 2003, D'Emanuele *et al*., 2004, Svenson *et al*., 2005 and Florence *et al*., 2005), and gene transfection (Dufes *et al*., 2005, Kim *et al*., 2006 and Bayele *et al*., 2006). In recent, dendrimers usage in drug delivery had attain great development and different types of dendritic macromolecules have been synthesized and investigated as a carrier for drug delivery (Patri *et al*., 2002), gene delivery (Schatzlein *et al*., 2005), targeting (Patri *et al*., 2005), solubilization (Gupta *et al*., 2006), diagnosis (Wiener *et al*., 1994), chemical catalysis (Wu *et al*., 2006) and as multivalent ligand for interesting biological applications (Heldt *et al*., 2004 and Svenson and Tomalia, 2005).This review article intends to provide the reader with a glimpse into the synthesis, types and important applications of dendrimers.

SYNTHESIS OF DENDRIMERS

The first synthetic procedure towards well defined branched structures was reported by Vogel's in 1978, who named this procedure a "cascade synthesis" .In the early 1980's, Denkewalter patented the synthesis of L-lysrine-based dendrimers (Denkewalter *et al*., 1981). The first dendritic structures that were exhaustively investigated and that received widespread attention were Tomalia's PAMAM (polyamidoamine) dendrimers (Tomalia *et al*., 1990) and newkome's "arborol" systems (Newkome *et al*., 1985). In the synthesis of dendrimers, monomers lead to a mono disperse polymer, tree like generational structure. There are 2 methods of dendrimer synthesis they are,

1. Divergent synthesis
2. Convergent synthesis

Divergent synthesis: The dendrimer is prepared from the core as the starting point and built up generation by generation. In the divergent reaction because of the incomplete reaction by end group will create structural defects which further prevent formation of next generation. Divergent name is derived from the manner in which dendrimer grows outward from the core. The higher generations of divergently constructed dendrimers always contain certain structural defects. To prevent side reaction and to force reactions to completion a large excess of reagent is required.

Convergent synthesis: The convergent synthesis starts from the surface and ends up at the core, where the dendrimer segments (dendron) are coupled together. Two of these end tips are attached to a branched monomer to form a dendron and the process is repeated until a desired size is reached. To the core molecule the interconnected branches are attached. To synthesize dendrimers is difficult because a repeated reaction which consists of many steps is needed to protect the active site even in both methods. That why these are obstacles to the synthesis of large quantities of dendrimers (Hawker *et al*., 1990).

Other alternative preparation methods have been developed that aim to reduce the number of synthetic and purification steps and increase yields, such as the double-stage convergent growth approach (Labbe *et al*., 1996 and Ihre *et al*., 1998), double-exponential dendrimer growth approach (Kawaguchi *et al*., 1995), and orthogonal coupling (Zeng *et al*., 1996).

TYPES OF DENDRIMERS

Now days, dendrimers with different designed functionalities have become objects of particular academic and practical interest because of their unique superbranched structural, symmetrical shapes, good monodispersity and peripheral functionalities,. Here, some of the dendrimers having different functionalities are briefly described.

PAMAM dendrimer: The PAMAM (polyamidoamine) dendrimers are synthesized up to generation 10 (G10) by the divergent method starting from ammonia or ethylene diamine initiation cone reagents (fig. 1). They are constructed using a reiterative sequence consisting of a double Michael addition of methyl acrylate to a primary amino group followed by amidation of the resulting carbomethoxy intermediate with a large excess of ethylene diamine. Many surface modified PAMAM dendrimers are non-immunogenic, high water solubility and modified terminal-arms amine functional groups for binding various targeting or guest molecules. PAMAM dendrimers generally display concentration-dependent toxicity and haemolysis. PAMAM dendrimers with their amide backbones undergo hydrolytically degradation at physiological temperatures only on harsh conditions (Lee *et al*., 2005). The internal cavities of PAMAM dendrimers with tertiary amines and amide linkages can host metals or guest molecules to produce a unique functional architecture. PAMAM dendrimers are the most extensively reported moiety for almost all existing applications of dendrimers.

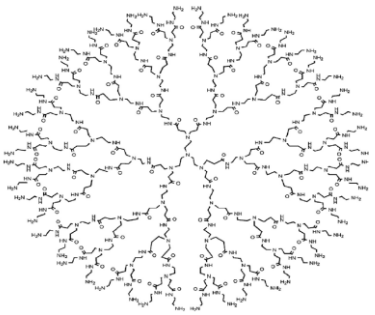

Fig. 1: PAMAM dendrimers

PPI dendrimers: PPI (polypropyleneimines) dendrimers (fig. 2) were created by Meijer at DSM of the Netherlands (DeBrabander-vandenBerg *et al*., 1993). PPI dendrimers up to generation 5 are synthesized by the divergent method starting from 1, 4. diamino butane. They grow by a reiterative sequence consisting of (A) a double Michael addition of acryloritrile to the primary amino groups followed by (B) Hydrogenation under pressure in the presence of Raney cobalt. Today, these PPI dendrimers are synthesized in large quantities by DSM and are commercially available. DSM uses its own designation to describe its dendrimers, where the core is diaminobutane, dendrindictes the interior dendritic branch cell; and n is the number of end groups.

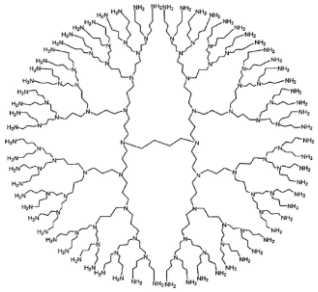

Fig. 2: PPI dendrimers

Liquid crystalline dendrimers: These are mesogenic (liquid crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers. Functionalization of end group of carbosilane dendrimers with 36 mesogenic units, attached through a C-5 spacer, leads to liquid crystalline dendrimers that form broad smetic A phase in the temperature range of 17–130C (Lorenz *et al*., 1996). Boiko *et al*.,. had synthesized first photosensitive liquid crystalline dendrimer with terminal cinnamoyl groups (Boiko *et al*., 1996). They have confirmed the structure and purity of this LC dendrimer by 1H NMR and GPC methods. Dendrimers under UV irradiation, can undergo E-Z isomerisation of the cinnamoyl groups and [2 + 2] photocycloaddition leading to the formation of a three-dimensional network.

Tecto dendrimers: Tecto-dendrimers are composed of a core dendrimer, which may or may not contain the therapeutic agent, surrounded by dendrimers of different types, each type designed to perform a function necessary to a smart therapeutic nanodevice (Betley *et al*., 2002). The Michigan Nanotechnology Institute for Medicine and Biological Sciences (M-NIMBS) are developing a tecto dendrimers which are used to perform the functions like diseased cell recognition, drug delivery, diagnosis of disease state, reporting location and outcome of therapy. The future planning was to produce a smart therapeutic nanodevice for the diseased cell like a cancer cell or a cell infected with a virus.

Chiral dendrimers: In chiral dendrimers the construction of core was based on different constitution but with similar chemical branches. Asymmetric catalysis and chiral molecular recognition are the main applications of chiral, nonracemic dendrimers (Ritzén and Frejd, 1999).

PAMAMOS dendrimers: PAMAMOS (poly amidoamine-organosilicon) are radially layered, inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors. These are exclusively useful for the preparation of honeycomb like networks with nanoscopic PAMAM and OS domains (Dvornic *et al*., 2000).

Hybrid dendrimers: Hybrid dendrimers are combination of dendritic and linear polymers in hybrid block or graft copolymer forms. The small dendrimer segment coupled to multiple reactive chain ends provides an opportunity to use them as surface active agents, compatibilizers or adhesives, e.g. hybrid dendritic linear polymers (Jain and Khopade, 2001).

Peptide dendrimers: Peptide dendrimers are defined as dendrimer containing peptides on the surface of the dendrimer frame work with amino acids as a branching (or) core unit. Peptide dendrimers with their peptide molecule had excellent compatibility in biological and therapeutical levels make them a potential candidate for various drug delivery systems. The main applications of the peptide dendrimers includes cancer, antimicrobials, antiviral, central nervous system, analgesia, asthma, allergy, Ca^{+2} metabolism, magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and serodiagnosis (Bruckdorfer *et al*., 2004 and Crespo *et al*., 2005).

Glycodendrimers: Dendrimers that incorporate carbohydrates into their structures are termed as glycodendrimers. Glycodendrimers are three types (i) carbohydrate-coated; (ii) carbohydrate centered; and (iii) fully carbohydrate-based. Glycodendrimers have been used to study the protein–carbohydrate

interactions that are in many intercellular recognition events. The main applications of glycodendrimers are study of protein–carbohydrate interactions, incorporation into analytical devices, gel formulation, MRI contrast agents, and gene delivery systems (Colinger, 2002 and Turnbull and Stoddart, 2002).

APPLICATIONS OF DENDRIMERS

Dendrimers have attracted the most attention as potential drug delivery scaffolds due to their unique characteristics. Dendrimers have narrow polydispersity; nanometer size range of dendrimers can allow easier passage across biological barriers. Dendrimers can be used to deliver drugs either by encapsulating the drug in the dendrimer interior void spaces or by conjugation to surface functionalities. All these properties make dendrimers as suitable carrier for drug delivery.

Dendrimers in transdermal drug delivery: Now day's dendrimers had key role for the improvement transdermal drug delivery system. In transdermal dosages drug delivery is difficult because of the hydrophobic nature and inefficient cell entry. Highly water soluble dendrimer are designed which improve the drug solubility, plasma circulation, and entry to cells make efficiently delivery drug from transdermal formulation.

Non-steroidal anti-inflammatory drug (NSAIDs) used for acute and chronic rheumatoid and osteoarthritis are limited there clinical usage by adverse events such as dyspepsia, gastrointestinal bleeding and renal side effects when give orally. Transdermal formulation will overcome adverse events and also provide good therapeutic blood level maintains for longer time. But poor rate of transcutaneous delivery pulls down transdermal delivery system. Drug permeation through the skin was enhanced by PAMAM dendrimer complex with NSAIDs (Ketoprofen, Diflunisal) as skin penetration enhancers. Permeation studies on rat skin were carried out for ketoprofen and diflunisal drug. High permeation was achieved by drug dendrimer complex (ketoprofen 3.4times and diflunisal 3.2times) when compared to drug. Antinociception effect of ketoprofen shows that dendrimer complex reduced writhing for period 1-8hr but drug reduced writhing up to 4-6hr.

In another study indomethacin and PAMAM dendrimer investigated (Chauhan *et al*., 2003). *In-vitro* and *in-vivo* studies were carried out for PAMAM dendrimer complex. *In-vivo* pharmacokinetic and pharmacodynamic studies in Wistar rats showed that significant higher concentration and effective concentration could be maintain for 24h in blood by G4 dendrimer indomethacin transdermal formulation.

Various transdermal penetration enhancers based on chemical and physical approach were carried out chemical penetration enhancers such as sulfoxide, oxazolidionesis, fatty acids essential oil, pyrrllidoions, terpenes and terpenoirds were used. Inotophoresis, electrophoresis, ultrasound, gel and patch are physical penetrates which used to exchange absorption of drug (Pathan and Setty, 2009, Santander-Ortega *et al*., 2010 and Shembale *et al*., 2012).

Recently Zhao *et al*., conjugated PEGylated PAMAM dendrimers for transdermal delivery of bioactive molecules delivery of bioactive by pre-treatment or co treatment technique using different vehicle lime water, chloroform isopropyal myristal chloroform water mixture and octanal water mixture emulsion. Further he reviewed the three different mechanisms which use to deliver the bioactives (Sun *et al*., 2012).

In another study Welowie *et al*., used that PAMAM dendrimers to conjugate 8-methoy psiralae (a photo sentizier for puva therapy). Here solubility of 8-methoxypsiralane PAMAM conjugate increased. Moreover in another study solubility of riboflavin was enhanced with increase in generation of PAMAM dendrimers. Moreover diffusion of riboflavin in pig ear skin was enhancing with increase in generation (Borowska *et al*., 2010). Moghmin *et al*., show that furful permeation enhances through rat skin model using pamam dendrimers (G5) in water vehicle by pretreatment (Moghimi *et al*., 2010).

Yang *et al*., reported that smaller G2 pamam dendrimers penetrate the skin layers more efficiently than the larger ones (G4). Increased skin absorption and retention were produced by G2 dendrimeric olic acid conjugates because of their increase in partition coefficient. Here permeation across skin layers is directly based on the size, surface charge and hydrophobicity of PAMAM dendrimers (Yang *et al*., 2012).

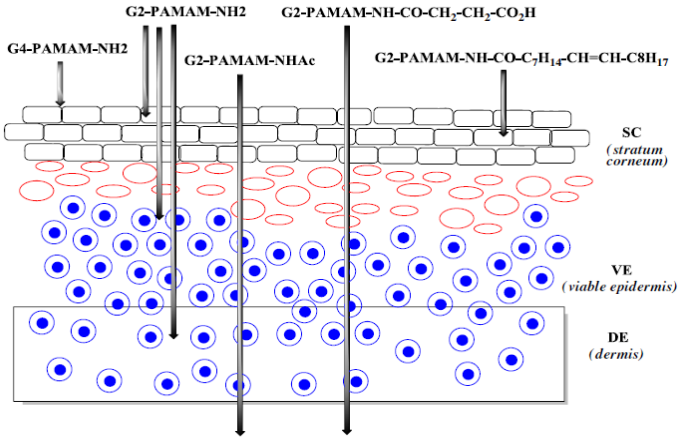

Fig. 3: Schematic representation of the internalization mode of PAMAM dendrimers with different surface attachments (Yang *et al*., 2012).

In transdermal applications nanoparticles (polysacchird and dendrimers) are used to increase the potential of transdermal drug delivery system. Permal and co had extensive research work on dendrimer application in transdermal system they reveal that physico chemical properties of dendrimers play a vital role in delivery of drug by increase the penetration (Venuganti *et al*., 2009).

Therefore data suggested that dendrimer drug complex make transdermal delivery system was effective and might be a safe and efficacy method for treating different diseases (Cheng *et al*., 2007).

Dendrimers in oral drug delivery: Traditional Oral drug-delivery system has been the dominant route for many years because of its significant advantages. A major challenge for drugs is the possibility of oral delivery, but main drawback was the limited drug transport across the intestitinal epithelium due to their large size relative to the tight epithelial barrier of the gastrointestinal tract. Duncan's and his research group showed that macromolecules of 3nm diameters could penetrate through the rat's intestinal membranes, which allows *G*2.5-*G*3.5-PAMAM dendrimers to transport across the intestine (Duncan and Izzo, 2005). Moreover the acidic nature of the GI-tract enzymes and stomach can affect the drug and the nanocarrier. D'Emanuele group investigated effect of dendrimer generation and conjugation on the cytotoxicity, permeation and transport mechanism of surface-modified cationic *G*3-PAMAM propranolol dendrimer conjugation across Caco-2 cell monolayers (D'Emanuele *et al*., 2004). They suggested that the route of propranolol transport was initially transcellular, while the conjugate was able to bypass the P-gp efflux transporter, and they arrived as the same inference as above concerning the penetration pathway of the intestinal membrane. Najlah investigated transepithelial permeability of naproxen, a low solubility drug (Najlah *et al*., 2007). Stability studies of G0 PAMAM conjugates in 50% liver homogenate was compared to that in 80% human plasma showed the lactate ester linker gave prodrug of elevated stability in plasma with sluggish hydrolysis in liver homogenate. So, these conjugations exhibit potential nanocarriers for the enrichment of oral bioavailability. The Cheng and Xu group, reviewed that a PAMAM dendrimer complex of the anti-inflammatory drug ketoprofen sustained antinoninceptive activity (inhibit rate > 50%) until 8 h of oral administration to Kunming mice, whereas this activity was absent with the free drug after 3 h (Na *et al*., 2006). Increase in permeability and cellular uptake was produced by *G*4- PAMAM 7-ethyl-10-hydroxycamphtothecin complexation with respect to free 7-ethyl-10-hydroxycamphtothecin. They reported that complex has the potential to improve the oral bioavailability of drug.

Lin *et al*., carried out study on effects of PAMAM dendrimer in intestinal absorption of poorly absorble drug such as 5(6)- carboxyfluorsin isothicynate dextran, calctitonin and insulin in rat (Lin *et al*., 2011). Drug carboxylorescin and calcitonin showed increase in absorption in rats small intestine for 0.5%w/v G2 PAMAM dendrimer complex. But fluorescine isothiocynate dextran and insulin had not produced any desirable effects. Moreover absorption in small intestine is mainly base on molecular weight of drug ie the molecular weight of drug increase absorption of drug decreases.

Recently Kolhatkar *et al*., explored oral delivery of SN – 38 (a potent topisomers –I inhibtor) and active metabolize of irinotecan hydrochloride (cpt-11) was improved by conjugation with G4 PAMAM dendrimer.10 fold increase in $caco_3$ cell monolayer and 100 fold increase in cellular uptake

by SN-38 and G4 PAMAM dendrimer than plain drug (Kolhatkar *et al*., 2008) .

Dendrimers in targeted drug delivery: Targeted drug delivery system had fetched great importance in the pharmaceutical field mainly because it create wide scope in utilization of existing drug and reduced in draw backs. In treatment of cancer and tumour existing drug molecules are ineffective because of the cytotoxicity nature. The main reason for cytotoxicity is low molecule weight and high pharmacokinetic volume of distribution, quick elimination, so high dose of drug is required for the desired therapeutic effect which ultimately leads to high toxicity and unwanted harmful effects, moreover when these drug administered alone will develop high resistance and lack of specification will produce toxicity effect on the other healthy cells. Further these chemopathetic drugs had poor solubility and low bioavailability. Moreover these drug formulations are formulated with toxic solvents to produce effect dosage forms.

Above mentioned problems are overcome by the usage dendrimers as a carrier for delivery the drug in targeted manner. Dendrimers are able to produced specific targeting of drug to cells and thereby improving efficacy minimising side effects. Various research works are carried to prove that dendrimers can able to deliver the drug to the targeted tissue in controlled manner. Cisplatine was conjugate with pamam dendrimer by Malik *et al* (Malik *et al*., 2000). The conjugate shows increased solubility, reduced toxicity and EPR properties. It was observed that this formulation showed superior activity over cisplatin when injected into mice bearing B16F10 tumor cells.

Doxorubicin is complexed with 2-3-bis (hydro methyl) proxamic acid dendrimers and characterise for *in-vitro* and *in-vivo* studies. The complexation of drug with dendrimer mainly by covalently bond through hydrazone linkage to high molecule weight 3-arm polyethylene oxide, exhibits reduced cytotoxicity *in-vitro*. But *in-vivo* studied shows minimum accumulation in vital organs and increase half life for conjugate drug compared to free drug. Jesus and group had concluded that dendrimer formulation increase half life of the drug and there reduced the amount of drug administered (De Jesus *et al*., 2002).

The *in-vivo* characterize in the mice of dendrimer conjugate should increased solubility, reduced toxicity and EPR properties when compared with free drug. Dendrimer conjugate of Cisplatine produced superior activity in targeted manner when compared with free drug. Poly amide amine dendrimers was conjugated with 1-bromoacetyl-5-flurouracil to produce dendrimer 5Fu-conjugates. Zhou *et.al* demonstrated that release of the drug from the dendrimer was base on generation and further indicates that dendrimer are promising drug for targeted drug delivery (Zhuo *et al*., 1999).

Dendrimer conjugates showed good elimination compared with drug in *in-vitro* studies carried out in the mice by Lee group. Doxurubin model drug was conjugated with polyester based dendrimer. Dendrimer-PEO-doxorubine conjugate inhibit the growth of C-26 tumor which was implanted subcutaneously in mice (Lee *et al*., 2006).

Anti-cancer drugs 5-Flurouracil was conjugated with pamam dendrimer to measure its activity through blood level studies in the mice. Dendrimer formulation had increase drug loading capacity and stability with reduction hemolytic toxicity (Bhadre *et.al* 2003). In another study by Asthan in 2005 had confirmed that pamam dendrimer had increase residence time, good stability and increase the half life of drug. They perform *in-vivo* studies in rat with flurbiprofan loaded pamam dendrimer conjugates which reveals that drug release from dendrimer is rapid in initial and slow release in latter stage (Asthana *et al*., 2005). In the same year imaging and targeting of tumor cells by using pamam dendrimer was carried out by the choi groups. They formulated pamam dendrimer conjugated with folic acid as targeted drug fluorescein isothiocyanate as imaging agent by oligonucleotides linkage. They conform that dendrimers can be used as imagine and drug targeting simultaneously (Choi *et al*., 2005).

The galactose linked PPI dendrimer was conjugated with primaquine phosphate and subjected for *in-vivo* testing to find out accumulation in the rat liver. Galactose linked PPI dendrimer with primaque phosphate showed less accumulation in the liver which compared the free drug and uncoated PPI dendrimer. These results had showed that coating of PPI dendrimer can improve the effective delivery of drug and reduced toxicity there by increasing the stability (Bhadra *et al*., 2005). Kukowska-Lattalo et al synthesis the dendrimers conjugated with folic acid and methotrexate. An *in-vivo* study in mice was carried out to conclude that dendrimer conjugated are more effective then free drug. In confocal microscopic image showed consider numbers of cells are targeted by dendrimeric conjugate and this results where further confirmed by analysis of isolated tumour cells (Kukowska-Latallo *et al*., 2005).

Doxorubicin was taken as model drug and conjugated with 6^{th} generation cationic poly-L-lysine dendrimers. The dendrimer conjugate had a increase penetration and delay in growth of prostate 3D multicellular tumor spheroids (MTS) compared

with free drug (Khuloud *et al*., 2013). Xiangyang Shi *et al*., had synthesis conjugate of pamam dendrimer with anti cancer drug 2-methoxyestradiol. The dendrimer conjugated release drug in sustained manner and specifically targeted the cancer cells in MTT assay. This study makes dendrimer as one of the novel carrier for anticancer drug (Yin *et al*., 2011).

Umesh Gupta *et al.*, explore potential delivery activity PPI dendrimer and folated conjugated PPI dendrimer. Doxorubine was used as model drug. The folate conjugated PPI shows faster drug release in acidic environment and high cell uptake in MCFT cancer cell line compared with PPI dendrimer. So it had been conclude that folic acid conjugated PPI dendrimer are better carrier agents (Gupta *et al*., 2010). Garcia-vallejo *et al.*, synthesis pamam dendrimer conjugated with leb. The characterisation of dendrimer conjugated showed enhanced binding, optimal internalisation, increase lysosomal delivery, increase antigen presentation and cytokine response. It had been conclude that dendrimer can be used for targeting peptide antigen cancer immunotherapy, auto immunity and infectious disease (García-Vallejo *et al*., 2013).

Pamam dendrimer of generation 5^{th} was conjugated with N-acetylgalactosamine via peptide and thiourea linkage. Hepatic cell line studies showed that dendrimer conjugated had increase cellular uptake by ASGPR mediated endocytosis. Moreover increase in concentration of dendrimer produced more effective cell targeting. The dendrimer conjugated produced Michaelis menten kinetics. It had concluded that dendrimer conjugate are effectively used as targeted carrier for hepatic targeting (Scott *et al*., 2011).

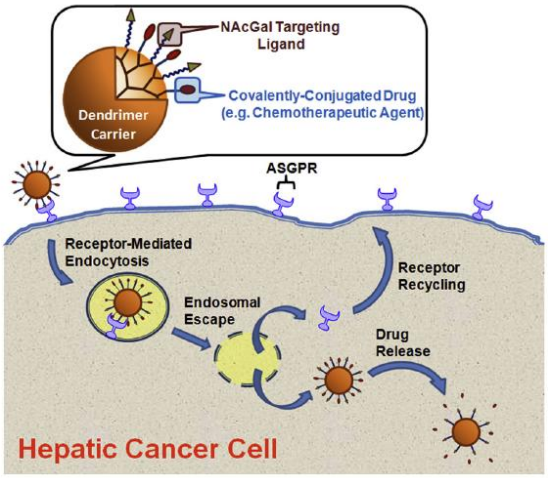

Fig. 4: A schematic drawing showing the composition of a drug-loaded G5-NAcGal conjugate binding to the ASGPR expressed on the surface of hepatic cancer cells (e.g. HepG2), which triggers receptor-mediated endocytosis of these G5-NAcGal conjugates followed by endosomal escape and release of the therapeutic cargo into the cytoplasm while the ASGPR recycles back to the cell surface (Scott *et al*., 2011).

Anupama *et al*., synthesized 4.0 G PAMAM dendrimer and conjugated with Gallic acid [GA] for cancer targeted drug delivery system (Anupama *et al*., 2011). The Cytotoxicity study in MCF-7 cell line showed dendrimer conjugates had showed increase activity on cells.

Dendrimers in gene delivery: Gene therapy is one novel approach to cure the chronic disease. In this therapy the defective gene which is responsible for the over expression or under expression corrected. The gene therapy is mainly based on vector used because it will decide the success of gene therapy. Dendrimers are ideal vector in the gene delivery. Dendrimer are more stable, monodispersity, generation, modification in terminal and size of the dendrimer are controlled. Above mention properties made the dendrimer as one the vital carrier for the gene delivery.

Pamam starburst dendrimers were complexed with DNA through ethidium bromide. As the generation of the dendrimers increase the DNA regions also increase (Kukowska-Latallo *et al*., 2000). Kukowska-catallo et al synthesised G9 pamam dendrimer pCF1CAT plasmid complex. Intravenous administration of dendrimer complex in rat show high level of expressions in lung tissues. In another study a cyclodextrin surfaced G5 pamam dendrimer conjugate were produced by Kihara et al (Kihara *et al*., 2003). High level transgene expression was reported in intravenous administration in rat. In the same manner Wade *et al* developed manner coated pamam dendrimers as new transgene vector (Wada *et al*., 2005). In vitro studies should that mannose coated dendrimer conjugates showed high transfection dendrimer. Mamede *et al*., used 111In-oligo/G4100 and 111In-oligo/G4-bt-

Av100 as gene transfer vectors and in vivo biodistribution evaluation showed more accumulation in kidney and lung when compare to liver (Mamede *et al*., 2004). Furthers authors summarized that the positively charged DNA/dendrimer complexes condensed to form complexes of several nanometres and resulted in uptake by lung tissues.

A study by Schatzlein *et al*., showed surface treatment of PPI dendrimers with methylated quaternary amines improved the DNA complexation and decreased cytotoxicity (Schatzlein *et al*., 2005). PPI dendrimers of various generation acts as transfection agents and target gene efficiently expressed in the liver were studied by Dufes and groups (Dufes *et al*., 2005). They demonstrated that intravenous administration of a gene medicine and G3 PPI dendrimer complex could result in intratumoural transgene expression and regression of the established tumours in all animals.

Arginine peptide dendrimer of 5^{th} and 6^{th} generation was developed by Zhongwei group. Further characterization of dendrimer conjugates showed high transfection and high biosafety compared branched polyetherimide (PEI) on all cells in breast tumor models (Kui *et al*., 2012). Another study by Bing and co synthesized β-cyclodextrin complexed PAMAM dendrimer with human neuroblastoma SH-SY5Y cells. Dendrimer conjugates showed low cytotoxicity and high transgene activity compared with PAMAM (G 4)/pDNA complex (Bing *et al*., 2013).

A comparative study was carried out by Ajay and co between PAMAM G4 dendrimers and the surface modified dendrimers was conducted in HEK 293T, GM7373 and NCI H157G cell lines in gene transfer (Ajay *et al.*, 2010). Effect of excess of ornithine (100μM) on transfection efficiency of the ornithine-conjugated PAMAMG4 dendrimers was investigated in separate experiment. Transfection efficiency of PAMAMG4-ORN60 dendrimer complex was slightly higher in cancer cells (NCI H157G) as compared to HEK 293T cells. Transfection efficiency of the PAMAMG4-ORN60 dendrimers decreased in presence of excess of ornithine while there was no effect on the parent PAMAMG4 dendrimers. Jose *et al*., produced conjugates of plasmid DNA and PAMAM dendrimer G5 for gene delivery (Jose *et al*., 2010). Further characterization of dendrimer conjugates showed high efficiency in the gene expression.

Kui *et al*., synthesis different generations of dendritic poly(L-lysine) vectors for in vitro gene transfection (Kui *et al*., 2011). The higher generations tended to produce the greater positive potentials, indicating a stronger potency of the complexes to interact with negatively charged cell membranes. Dendrimer conjugates of 5^{th} generation showed good biocompatibility and higher efficiency transfection compared with other generation dendrimer complex.

Based on these results, we concluded that dendrimers were one of promising gene vectors which might be able to deliver gene into liver, spleen, lung, kidney, and even the tumor at therapeutic levels.

Dendrimers in pulmonary drug delivery: Bai and groups investigated Enoxaparin PAMAM dendrimers complex for pulmonary drug delivery (Bai *et al*., 2006). In this research enoxparin-PAMAM dendrimer complex were formulated and evaluated for the drug enachment. The dendrimer formulation was administered into lungs of anaesthetized rats and drug absorption was observed by measuring plasma anti-factor Xa activity, and by observing prevention efficacy of deep vein thrombosis in a rodent model. Bioavailability of enoxaparin was increased to 40% in G2 and G3 PAMAM dendrimers which are positively charged. They reported that positively charged dendrimers are suitable carrier for pulmonary delivery of Enoxaparin.

Seabrook and coworkers described the boosting effect with intranasal dendrimeric Aβ1-15 (16 copies of Aβ1-15 on a lysine tree) but not Aβ1-15 peptide affording immune response following a single injection of Aβ1-40/42 in heterozygous APP-tg mice (Seabrook *et al*., 2006).

Inapagolla *et al*., carried study on *in-vivo* efficacy of methylprednisolon conjugate G4 PAMAM dendrimers showed good lung anti inflammation potency (Inapagolla *et al*., 2010). Further methylprednisolon-G4-PAMAM dendrimers conjugate at the dose of 5mg/kg improved the airway delivery in pulmonary inflammatory model based on a 11 fold enchament of eosinophil lung accumulation following five daily inhalation exposure of sensitized mice to allergen and albumin. Here allergen induced inflammation reduced by drug loaded dendrimer conjugate was mainly base on improved drug residence time in the lung.

Dong *et al*., carried out invivo pulmonary absorption on for G0-G3 PAMAM dendrimers conjugates of insulin and calction. Here absorption of insulin and calction was increased by PAMAM dendrimers conjugates. Moreover absorption rate was increased as generation of PAMAM increases (Dong *et al*., 2010).

To target regional lung deposition dendrimers emerged has very powerful carries in nano size. Review paper by carvalho *et al*., and choi

et al., has explained the important and influence of particle size, charge, and coating on lung deposition (Carvalho *et al*., 2011 and Choi *et al*., 2010). Dendrimers did posses characteristic to emerge as nanocarrier for delivery bioactives through inhalation route.

CONCLUSION

The application of dendrimers to drug delivery system has experienced rapid growth. Dendrimers are expected to play key role in pharmaceutical field as drug carriers. Dendrimers role in the biomedical applications is widely expanded. The supramolecular properties of the dendrimers made them major agent to delivery drugs and other function. As per reviewed in this article dendrimers are widely used in encapsulation various drugs and to deliver the drug to the targeted site. More over high level of controllable features of dendrimers such as size, shape, branching length and surface modifications make them an ideal drug carrier. Further dendrimers offer generation number and terminal groups and the chance to introduce two or more functional group types at the periphery are mammoth advantages of dendrimers over polymers. Few drawbacks like toxicity, localization, bio-distribution and costly synthesis step pull them down. In spite of above drawbacks, several dendrimers have already been commercialized, and some are in clinical trials. To make dendrimers commercial successful tool for drug delivery more research work has to be done on cost effective synthesis, toxicity reduction and drug conjugation. As reviewed in this article dendrimer moiety hold great promise and potential tool for drug delivery system.

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