REVIEW ARTICLE ISSN: 2249-3387

AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

DENDRIMERS: SYNTHESIS, PROPERTIES, BIOMEDICAL AND DRUG DELIVERY APPLICATIONS.

Sougata Jana[1*], Arijit Gandhi[1], Kalyan Kumar Sen[1], Sanat Kumar Basu[1]

1. Department of Pharmaceutics, Gupta College of Technological Sciences, Ashram More, Asansol-713301, West Bengal, India.

ABSTRACT

Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse macromolecules. The structure of these materials has a great impact on their physical and chemical properties. As a result of their unique behaviour dendrimers are suitable for a wide range of targeted drug delivery, controlled drug delivery, gene delivery and industrial applications. The paper gives a concise review of dendrimers physico-chemical properties, types, synthetic pathway & their possible use in various aspects of research, technology and treatment of disease.

Key words: Dendrimer, targeted drug delivery, gene delivery, dendrimer synthesis, dendrimer properties, dendrimer types.

INTRODUCTION

Polymer chemistry and technology have traditionally focused on linear polymers. Recently it has been found that the properties of highly branched macromolecules can be very different from conventional polymers. The unique structural features of dendritic macromolecules have number of chains whose ends combined with a high degree of branching which leads to a variety of new physical properties when compared with traditional linear polymers. Dendrimer chemistry was first introduced in 1978by FritzVogtle & Coworkers[1]. He synthesized the first cascademolecules.

*Corresponding Author Email: janapharmacy@gmail.com

Received 27 November 2011, Accepted 10 December 2011

Please cite this article in press as: Sougata J *et al.*, Dendrimers: Synthesis, Properties, Biomedical and Drug Delivery Applications. American Journal of PharmTech Research 2012.

In 1985, Donald A. Tomalia, synthesized the first family of dendrimers. The word *"dendrimer"* originated from two words, the Greek word *dendron*, meaning tree, and *meros*, meaning part [2]

They are synthetic nanomaterials that are approximately 2-10 nm in diameter. They are hyper branched and monodisperse three-dimensional molecules with defined molecular weights, large numbers of functional groups on the surface and well-established host-guest entrapment properties. They are made up of layers of polymer surrounding a central core (figure1). The dendrimer surface contains many different sites to which drugs may be attached and also attachment sites for materials such as polyethylene glycol (PEG) which can be used to modify the way the dendrimer interacts with the body [3, 4]

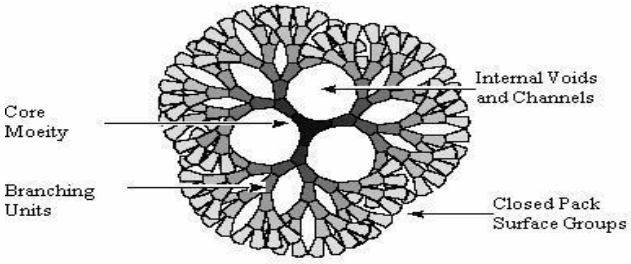

Figure 1: structure of dendrimer

Synthesis of dendrimers:-

Since 1979, Dendrimers are generally prepared using two major strategies. The first was introduced by Tomalia, called as "divergent method" in which growth of dendrimers originates from a core site[5]. The second method, pioneered by Hawker and Fréchet follows a "convergent growth process". In which, several dendrons are reacted with a multifunctional core to obtain a product[6].

In the **divergent methods,** dendrimer grows outwards from a multifunctional core molecule. The core molecule reacts with monomer molecules containing one reactive and two dormant groups giving the first generation dendrimer. Then the new periphery of the molecule is activated for reactions with more monomers. The process is repeated for several generations and a dendrimer is built layer after layer (Figure 2). Divergent approach is successful for the production of large quantities of dendrimers. Problems occur from side reactions and incomplete reactions of the end groups that lead to structure defects. To prevent side reactions and to force reactions to completion large excess of reagents is required. It causes some difficulties in the purification of the final product[7]

The convergent approach (Figure 3) was developed as a response to the weakness of divergent synthesis. Convergent growth begins at what will end up being the surface of the dendrimer, and

works inwards by gradually linking surface units together with more[9]. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. The advantage of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation adding step.

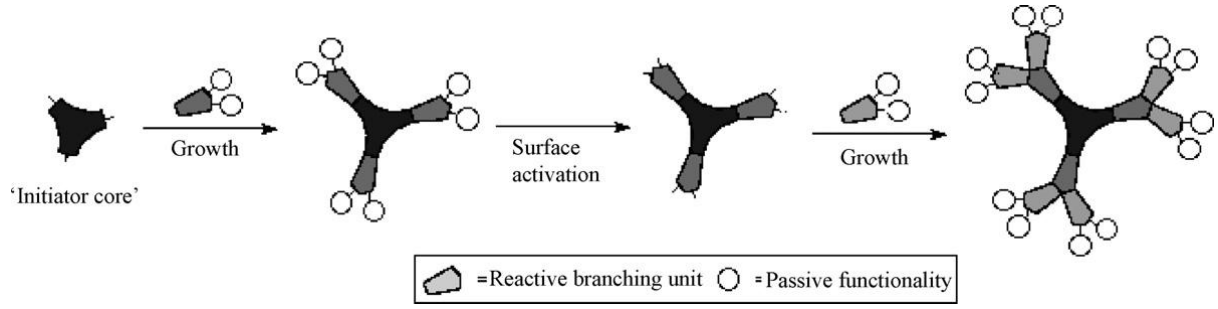

Figure 2: Divergent growth method [8].

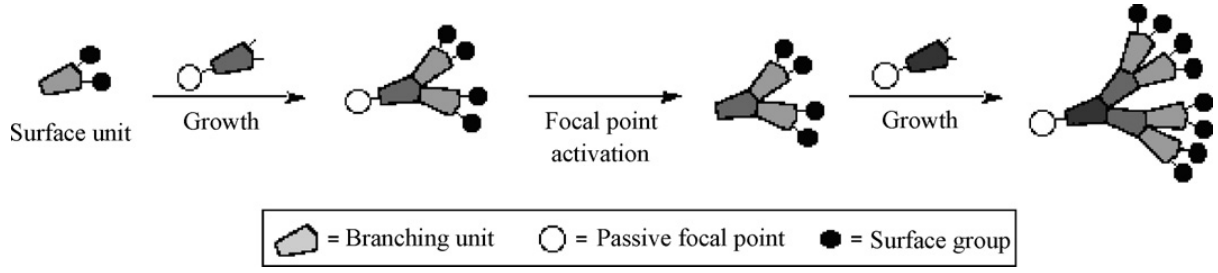

Figure 3: convergent growth method[10]

Recently a breakthrough in the practice of dendrimer synthesis has come with the concept and of **double exponential growth**. Double exponential growth, similar to a rapid growth technique for linear polymers. This approach allows the preparation of monomers of both convergent and divergent growth from a single starting material [11, 13]

The strength of double exponential growth is more subtle than the ability to built large dendrimers in relatively few steps. In fact, double exponential growth is so fast that it can be repeated only two or perhaps three times before further growth becomes impossible. This methodology provides a means whereby a dendrite fragment can be extended in either the convergent or divergent direction as required. In this way, the positive aspects of both approaches can be accessed without the necessity to bow to their shortcomings (Figure 4).

Properties of dendrimers:-

Dendrimers are the class of dendritic polymers that can be constructed with a well-defined molecular structure, i.e. being monodisperse, unlike to linear polymers. Jackson et al observed the monodispersity of dendrimers by high performance liquid chromatography (HPLC), size exclusion chromatography (SEC), mass spectrometry (MS), and gel electrophoresis and

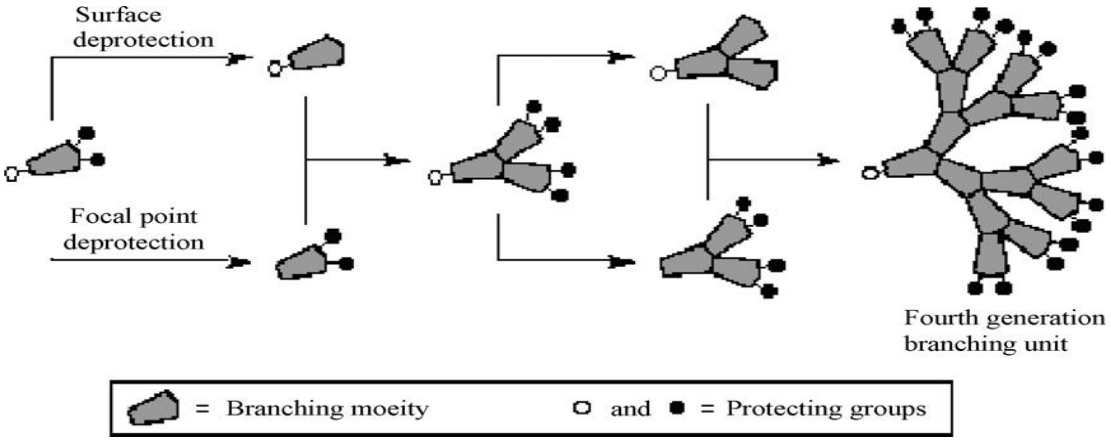

Figure 4: Double Exponential and Mixed Growth[14].

transmission electron microscopy (TEM) [15]. Based on their dimensional length scaling, narrow size distribution and other biomimetic properties, Svenson *et al* described dendrimers as an "artificial proteins"[16]. Cheng et al observed that within the PAMAM dendrimer family, the diameter of the generation 1–10 with ethylenediamine core increases from 1.1 to 12.4 nm[17]. Surfaces may be designed with functional groups to augment or resist trans-cellular, epithelial or vascular bio permeability. An interior void space may be used to encapsulate small molecule drugs, metals, or imaging moieties. Encapsulating in that void space reduces the drug toxicity and facilitates controlled release. Dendrimer solution has significantly lower viscosity than linear polymers. The presence of many chain-ends is responsible for high solubility and miscibility and for high reactivity. Solubility of dendrimers is influenced by the nature of surface groups. Dendrimers terminated in hydrophilic groups are soluble in polar solvents, while dendrimers having hydrophobic end groups are soluble in non polar solvents [18, 19]. X-ray analysis on dendrimer suggests that the molecular shape of the lower to higher generations becomes increasingly globular (i.e. more spherical compare to linear shaped), in order to spread out the larger molecular structure with a minimal repulsion between the segments[20]. These fundamental properties have in fact lead to their commercial use for gene therapy, immunodiagnostics and variety of other biological applications[21].To utilize dendrimers as biological agents, they have to fulfil certain biological demands such as non-toxicity, non-immunogenicity (except for vaccines), ability to cross bio barriers such as, the intestine, the blood–tissue barriers etc., ability to stay in circulation for the time needed to have a clinical effect; ability to target to specific structures etc.

The **advantage of dendrimers** is that they are well controlled during synthesis & therefore having lower polydispersity index. As the density of branches increases the outer most branches

arrange themselves in the form of spheres surrounding a lower density core and outer surface density is more and most of the space remains hollow towards core. This region can be utilized for drug entrapment. Outer surface of dendrimers has multiple functional groups, which can be used to attach vector devices for targeting to particular site in the body. They can be modified as stimuli responsive to release drug. Dendrimers might show an enhanced permeability and retention effect (depending on their mol. wt.) that allows them to target tumour cells more effectively than small molecules. They are ideal drug delivery systems due to their feasible topology, functionality and dimensions; and also, their size is very close to various important biological polymers and assemblies such as DNA and proteins [22, 24]

TYPES OF DENDRIMERS:-

Liquid crystalline dendrimers-

They consist of mesogenic (liq. crystalline) monomers e.g. mesogen functionalized carbosilane dendrimers. Lorenz et al. observed that functionalization of end group of carbosilane dendrimers with 36 mesogenic units, attached through a C-5 spacer, leads to liquid crystalline dendrimers [25]. Boiko et al. claims that they have synthesized first photosensitive liquid crystalline dendrimer with terminal cinnamoyl groups. Structure and purity of this liquid crystalline dendrimer were confirmed by 1H NMR and GPC methods. It was shown that such a dendrimer, under UV irradiation, can undergo E-Z isomerization of the cinnamoyl groups and photo cyclo-addition leading to the formation of a three-dimensional network [26].

Tecto dendrimers:-

Tecto-dendrimers are composed of a core dendrimer, which may or may not contain the therapeutic agent, surrounded by dendrimers. The surrounding dendrimers are of several types, each type designed to perform a function necessary to a smart therapeutic nano device Fig. 5 shows the PAMAM core–shell tecto dendrimer.

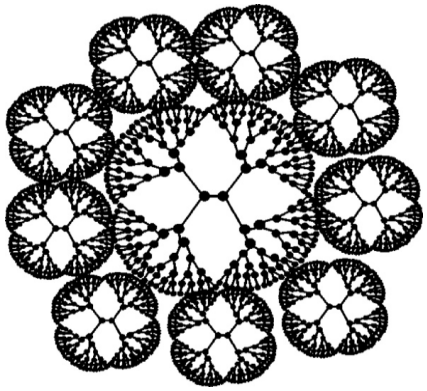

Figure. 5. Schematic representation of PAMAM core–shell tecto dendrimer [27]

Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

Chiral dendrimers:-

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core. Ritzén *et al* observed Chiral; nonracemic dendrimer with well-defined stereochemistry is particularly interesting subclass, with potential applications in asymmetric catalysis and chiral molecular recognition [28].

PAMAMOS dendrimers:-

Poly (amidoamine-organosilicon) dendrimers (PAMAMOS) are radially layered & they are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) in the interior and hydrophobic organosilicon (OS) in the exterior. These dendrimers are useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains[29].

Hybrid dendrimers:-

These are hybrids (block or graft polymers) of dendritic and linear polymers. The small dendrimer segment coupled to multiple reactive chain ends provides an opportunity to use them as surface active agents, compatibilizers or adhesives [30].

Peptide dendrimers:-

Dendrimers having peptides on the surface of the traditional dendrimer framework and dendrimers incorporating amino acids as branching or core units are both defined as 'peptide dendrimers'[31]. Peptide dendrimers play an important role in diverse areas including cancer, antimicrobials, antiviral, central nervous system, analgesia, asthma, allergy and Ca+2 metabolisms. On the basis of their ability to be taken up by cells, making peptides very useful for drug delivery. One more interesting application of peptide dendrimers is that can be used as contrast agents for magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), fluorogenic imaging and serodiagnosis [32, 33]

Glycodendrimers:-

The term 'glycodendrimers' is used to describe dendrimers that incorporate carbohydrates into their structures (Figure 6). Glycodendrimers can be carbohydrate-coated; carbohydrate centred or fully carbohydrate-based. Glycodendrimers have been used for a number of applications such as, glycodendrimers with surface carbohydrate units have been used to study the protein–carbohydrate interactions that are in many intercellular recognition events. The accessibility of

the sugars is an important consideration for glycodendrimers used effectively to evaluate protein–carbohydrate interactions. Like this, study of protein–carbohydrate interactions, incorporation into analytical devices, formulation of gels, targeting of MRI contrast agents, drugs and gene delivery systems are some of the areas where glycodendrimers are likely to be beneficial.

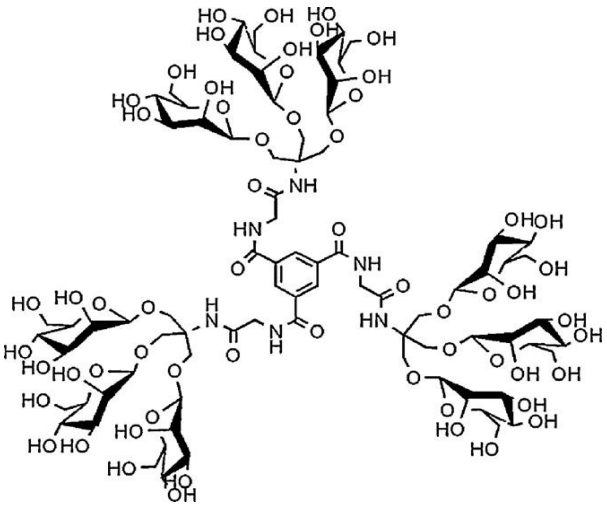

Figure 6: Carbohydrate containing glycodendrimers[34]

PAMAM dendrimer:-

Poly (amidoamine) dendrimers (PAMAM)(Figure 7) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents. Products up to generation 10 (a molecular weight of over 9, 30,000 g/mol) have been obtained (by comparison, the molecular weight of human hemoglobin is approximately 65,000 g/mol). PAMAM dendrimers are commercially available, usually as methanol solutions.

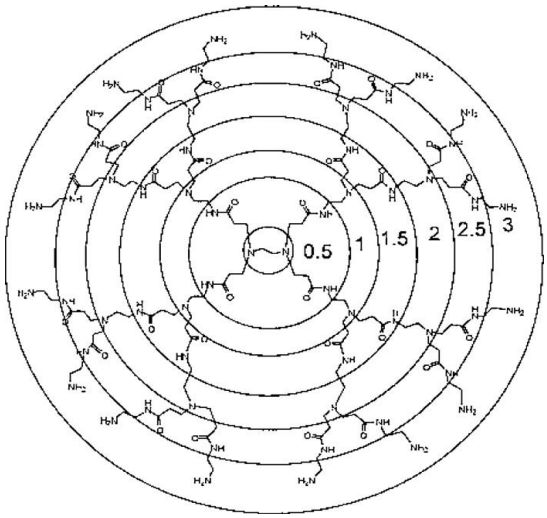

Figure 7: PAMAM generation 3 dendrimer

$NH_3 + 3CH_2CHCOOCH_3 \rightarrow N(CH_2CH_2COOCH_3)_3$ (1)

$N(CH_2CH_2COOCH_3)_3 + 3NH_2CH_2CH_2NH_2 \rightarrow N(CH_2CH_2CONHCH_2CH_2NH_2)_3 + 3CH_3OH$. (2)

Starburst dendrimers is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core [35, 36]. Many surface modified PAMAM dendrimers are non-immunogenic, water-soluble and possess terminal-modifiable amine functional groups for binding various targeting or guest molecules. PAMAM dendrimers are hydrolytically degradable only under harsh conditions because of their amide backbones, and hydrolysis proceeds slowly at physiological temperatures [37].

Multiple Antigen Peptide Dendrimers :-

It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points. This type of dendrimer was introduced by J. P. Tam in 1988, has predominantly found its use in biological applications, *e.g*. vaccine and diagnostic research[38].

APPLICATIONS OF DENDRIMERS:-

The development of an efficient drug delivery system is very important to improve the pharmacological activity of drug molecules. Dendrimers are new alternatives and efficient tools for delivery of drug molecules. As compare to linear polymeric carriers, the multivalent functionalities of dendrimers can be linked to drug molecules or ligands in a well-defined manner and can be used to increase the binding efficiency and affinity of therapeutic molecules to receptors via synergistic interaction [39]

Dendrimers as a carrier for drug delivery:-

Dendrimers have narrow polydispersity; nanometer size range of dendrimers can allow easier passage across biological barriers. All these properties make dendrimers suitable as host either binding guest molecules in the interior of dendrimers or on the periphery of the dendrimers.

Oral drug delivery:

Oral drug delivery systems are very important to the field of medicine, since most of the common illnesses are treated via oral rout of medication. There are also some defects of oral delivery route like low solubility in aqueous solutions and low penetration across intestinal membranes. Dendrimers are able to hold medication with good durability but also biodegradable within a biological system. Jevprasesphant *et al* investigated effect of dendrimer generation and conjugation on the cytotoxicity, permeation and transport mechanism of PAMAM dendrimer and

surface-modified cationic PAMAM dendrimer using mono layers of the human colon adenocarcinoma cell line [40].

Naha *et al* evaluated the immunotoxicity of three generations of polyamidoamine (PAMAM) dendrimers (G-4, G-5 and G-6) in mouse macrophage cells in vitro. Using the Alamar blue and MTT assays, a generation dependent cytotoxicity of the PAMAM dendrimers was found whereby G-6>G-5>G-4. The inflammatory mediators macrophage inflammatory protein-2 (MIP-2), tumour necrosis factor-α (TNF-α) and interleukin-6, (IL-6) were measured by the enzyme linked immunosorbant assay (ELISA) following exposure of mouse macrophage cells to PAMAM dendrimers. A generation dependent ROS and cytokine production was found, which correlated well with the cytotoxicological response and therefore number of surface amino groups. A clear time sequence of increased ROS generation (maximum at ~4 h), TNF-α and IL-6 secretion (maximum at ~24 h), MIP-2 levels & cell death (~72 h) was observed [41]. The family of dendrimers most investigated in drug delivery is the poly (amido amine) dendrimers (PAMAM). PAMAM dendrimers are biocompatible, non-immunogenic, water soluble and possess terminal modifiable amine functional groups for binding various targeting or guest molecules [42]. The high density of amino groups and internal cavities in PAMAM dendrimers is expected to have potential applications in enhancing the aqueous solubility of low solubility drugs [43, 45]. Generation 0.5 (G0.5) to generation 4 (G4) PAMAM dendrimers have been used to encapsulate and solubilise acidic drugs such as Nifedipine [46], Ibuprofen [47] and Indomethacin [48].Further, PAMAM derivatives modified by –OH or –COOH groups were found to encapsulate small hydrophobic guest molecules successfully: Twyman *et al.* [49] converted the ester terminated PAMAM dendrimers to a more soluble hydroxyl surface by reacting with TRIS (Tris (hydroxymethyl)aminomethane). The –OH-terminated dendrimers were found to increase solubility by weak hydrogen bonding; by Liang Ouyang *et al* [50] synthesized the PAMAM dendrimers with aspartate graft in peripheral and used these kinds of dendrimers as the enhanced solubility

Recently, more dendritic molecules were investigated as solubility enhancers such as poly-lysine (PLS) [51], polypropyleneimine (PPI) [52] .and poly-citric acid dendrimers (PCA) [53]. Several previous reviews have covered the early work of the solubility enhancement with dendrimers. The possible mechanisms of the dendrimer-mediated solubility enhancement are based on a typical dendrimers structure: (a) a central core with enough internal cavities is available to encapsulate the guest molecules; (b) branching units provide weak hydrogen bonding to increase

solubility; (c) the surface groups are mainly responsible for the solubility enhancement by electrostatic interactions [54–56]. Ketoprofen, a non-steroidal anti-inflammatory drug with well-known anti-inflammatory, antipyretic and analgesic properties, has low solubility in water and causes local or systemic disturbance in the gastrointestinal tract. In the present study we investigated the potential of polyamidoamine (PAMAM) dendrimers as drug carriers of ketoprofen by in vitro and in vivo studies. The in vitro release of ketoprofen from the drug–dendrimer complex is significantly slower compared to pure ketoprofen. Anti-nociceptive studies using the acetic acid-induced writhing model in mice showed a prolonged pharmacodynamic behaviour for the ketoprofen–PAMAM dendrimer complex[57].Sweet *et al* investigated transepithelial transport of PEGylated anionic poly (amidoamine) dendrimers. Cytotoxicity, uptake and transport across Caco-2 cells of PEGylated G3.5 and G4.5 PAMAM dendrimers were studied. Methoxy polyethylene glycol (750 Da) was conjugated to carboxylic acid-terminated PAMAM dendrimers at feed ratios of 1, 2 and 4 PEG per dendrimer. Compared to the control, PEGylation of anionic dendrimers did not significantly alter cytotoxicity up to a concentration of 0.1 mM. PEGylation of G3.5 dendrimers significantly decreased cellular uptake and transepithelial transport while PEGylation of G4.5 dendrimers led to a significant increase in uptake, but also a significant decrease in transport. PEGylated dendrimers show promise in oral delivery applications where increased functionality for drug conjugation and release is desired [58].

Ocular drug delivery:-

Application of active drugs to the eye is the most prescribed route of administration for the treatment of various ocular disorders& infections. It is normally accepted that the intraocular bioavailability of topically applied drugs is extremely poor, mainly due to drainage of the excess fluid via nasolacrimal duct and elimination of the solution by tear turnover. Several research work have been made in ocular drug delivery systems by using specialized delivery systems such as polymers, liposomes, or dendrimers to overcome these disadvantages. Ocular drug-delivery systems should be nonirritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable. Dendrimers provide unique solutions to minimize delivery problems for ocular drug delivery. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups. These surface-modified dendrimers were predicted to enhance pilocarpine bioavailability [59-61]

Transdermal drug delivery:-

Dendrimers have found applications in transdermal drug-delivery systems. Generally, those bioactive drugs having hydrophobic moieties in their structure, resulting in low water solubility & as a result efficient delivery into cells is inhibited. Dendrimers designed to be highly water-soluble and biocompatible have been shown to be able to improve drug properties such as solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently. Non steroidal anti-inflammatory drugs are very effective in the treatment of acute and chronic rheumatoid and osteoarthritis. Clinical use of NSAIDs is limited due to adverse reactions such as GI side effects, renal side effects when given orally. Transdermal drug delivery overcome these adverse effects and also maintains therapeutic blood level for longer period of time. Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) could be improving the drug permeation through the skin as penetration enhancers. The model drugs Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and investigated for different studies. In vitro permeation studies on excised rat skin showed 3.4 times higher permeation of Ketoprofen from Ketoprofen–dendrimer complex than that from 2mg/mL Ketoprofen suspended in normal saline. Similarly, a 3.2 times higher permeated amount was observed with Diflunisal–dendrimer complex. Anti-nociception effect of drugs was studied on mice; results showed that Ketoprofen–dendrimer complex reducing writhing activity during the period of 1–8 h after Transdermal administration, while pure Ketoprofen suspension at the equivalent dose of Ketoprofen significantly decreased number of writhing between 4 and 6 h after drug was transdermally given[62]. Chauhan *et al*. investigated transdermal ability of PAMAM dendrimers by using indomethacin as the model drug for study. In vitro permeation studies showed increase in the steady-state flux as increase in concentration of all three types G4-NH2, G4-OH and G-4.5 PAMAM dendrimers. For the in vivo pharmacokinetic and pharmacodynamic studies, indomethacin and dendrimer formulations were applied to the abdominal skin of the Wistar rats and blood collected from the tail vein at the scheduled time. The indomethacin concentration was significantly higher with PAMAM dendrimers when compared to the pure drug suspension. The results showed that effective concentration could be maintained for 24 h in the blood with the G4 dendrimer–indomethacin formulation. Therefore, data suggested that the dendrimer–indomethacin based transdermal delivery system was effective and might be a safe and efficacious method for treating various diseases [63.]

Pulmonary drug delivery:-

Dendrimers are used for pulmonary drug delivery also. During one study, efficacy of PAMAM Dendrimers in enhancing pulmonary absorption of Enoxaparin was studied by measuring plasma anti-factor Xa activity, and by observing prevention efficacy of deep vein thrombosis in a rodent model. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40%, while G2.5 PAMAM, a half generation dendrimers, containing negatively charged carboxylic groups had no effect. Formulations did not adversely affect mucociliary transport rate or produce extensive damage to the lungs. So the positively charged dendrimers are suitable carrier for Enoxaparin pulmonary delivery [64]

Dendrimers in targeted drug delivery:-

Nowadays general cancer chemotherapeutics are less efficacious to cure tumours because of the nonselective action drugs, resulting in dose limiting side effects. Use of carrier systems for targeting drugs to tumour cells is an alternative approach for treating cancer and offers both increased therapeutic index and decreased drug resistance. An effective targeting drug-delivery system requires a base that is uniform and able to couple multiple components such as targeting molecule, drug and cancer imaging agent [65]. Dendrimers have ideal properties which are useful in targeted drug-delivery system. Okuda et al synthesized a sixth generation lysine dendrimer (KG6) and two PEGylated derivatives thereof and evaluated their bio-distribution characteristics in both normal and tumor-bearing mice. The intact KG6 showed a rapid clearance from the blood stream and non-specific accumulation in the liver and kidney. In contrast, the PEGylated derivatives showed a better retention in blood and low accumulativeness in organs dependent of the rate of PEGylation. In addition, PEGylated KG6 with a high modification rate was accumulated effectively in tumor tissue via the enhanced permeability and retention effect. Moreover, we clarified that multiple administrations did not affect the bio-distribution characteristics of a second dose of PEGylated KG6. PEGylated lysine dendrimer would be a useful material for a clinically applicable tumour-targeting carrier [66.] PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. Further these two molecules are linked with complementary oligonucleotides. DNA-assembled nanoclusters were evaluated in vitro which helps in detecting tumor cell-specific binding and internalization. These DNA-assembled dendrimer conjugates may allow the combination of different drugs with different targeting and imaging agents so it is easy to develop combinatorial therapeutics[67]. Methotrexate (MTX), an antimetabolite and

antifolate drug used in the treatment of many cancers, acts by inhibiting the metabolism of folic acid. Methotrexate is a weak dicarboxylic acid, and therefore, mostly negatively charged at physiologic pH. Its mean oral bioavailability spans the range of 13–76%, while the mean intramuscular bioavailability is 76%. The higher doses of MTX often used in cancer chemotherapy can cause toxic effects to the rapidly dividing cells of bone marrow and gastrointestinal mucosa. Methotrexate has been encapsulated into generations 3 and 4 PAMAM dendrimers, which had PEG550 and PEG2000 monomethyl ether chains conjugated to their surfaces to modify bioavailability and toxicity. The encapsulation efficiency was dependent on PEG chain length and size of the dendrimer[68].The anticancer drug paclitaxel (PTX) is a mitotic inhibitor used in chemotherapy to treat patients with lung, ovarian, breast, and head and neck cancers as well as advanced forms of Kaposi's sarcoma. The drug works by interfering with normal microtubule growth during cell division, which especially affects fast growing cancer cells. In order to enhance its poor water solubility, paclitaxel has been encapsulated mainly into micelle-based formulations [69-72]. There is one recent study employing dendrimers as solubility enhancer. PTX encapsulation into polyglycerol dendrimers resulted in 400-fold improved water solubility compared to the pure drug [73] .However, most dendrimer-related formulations utilize PTX conjugation to the dendritic carrier (prodrug approach). L-DOPA (levodopa, 3, 4-dihydroxy-L-phenylalanine) is a prodrug capable of passing the blood–brain barrier and treating Parkinson's disease. It is decarboxylated in the brain to become dopamine, the neurotransmitter, by the enzyme aromatic-L-amino acid decarboxylase. However, it also induces side effects such as dystonia and dyskinesia after large doses or chronic use. Slow release of L-DOPA has shown reduction of the problems associated with its long-term therapy. L-DOPA was therefore converted into well-defined, monodisperse dendritic macromolecules. A third-generation L-DOPA dendrimer contained 30 L-Dopa residues, which made up its core, branches, and periphery. Individual L-Dopa moieties in the dendrimer were connected to one another via hydrolysable diester linkages. These Dopa dendrimers showed a 20-fold increase in aqueous solubility and enhanced photo stability in solutions over L-Dopa under identical conditions [74.]

Dendrimers for controlled release drug delivery:-

A third-generation micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release [75]. Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM dendrimers. Prepared dendrimer complexes observed that loaded drug displayed initial rapid release followed by slow release.

Pharmacodynamic study was performed using Carrageenan induced paw edema model [76]. The encapsulation of silver salts within PAMAM dendrimers produced conjugates exhibiting slow silver release rates and antimicrobial activity against various Gram-positive bacteria [77]. PAMAM dendrimers G4 with ethylenediamine (EDA) core and tris(2-hydroxymethyl)amidomethane (TRIS) surface and G5, EDA core with carboxylate surface, were used. Silver-containing PAMAM complexes were prepared by adding aqueous solutions of the dendrimers to the calculated amount of silver acetate powder.

Dendrimers in gene delivery:-

Dendrimers can act as carriers, called vectors, in gene therapy. Vectors transfer genes through the cell membrane into the nucleus. Currently liposomes and genetically engineered viruses have been mainly used for this. PAMAM dendrimers have also been tested as genetic material carriers. Cationic dendrimers (Polypropylenimine (PPI) dendrimer) deliver genetic materials into cells by forming complexes with negatively charged genetic materials through electrostatic interaction. Cationic dendrimers lend themselves as non-viral vectors for gene delivery because of their ability to form compact complexes with DNA. Santos et al synthesized a gene delivery vectors consisting of a medium-size generation PAMAM dendrimer (generation 5, with amine termini) core randomly linked at the periphery to hydrophobic chains that vary in length (12 to 16 carbon alkyl chains) and number (from 4.2 to 9.7 in average). The idea subjacent to the present work is to join the advantages of the cationic nature of the dendrimer with the capacity of lipids to interact with biological membranes. Unlike other amphiphilic systems designed for the same purpose, where the hydrophobic and hydrophilic moieties coexist in opposite sides, the present vectors have a hydrophilic interior and a hydrophobic corona. The vectors are characterized in respect to their ability to neutralize, bind and compact plasmid DNA (pDNA). The complexes formed between the vectors and pDNA are analyzed concerning their size, ζ-potential, resistance to serum nucleases, capacity of being internalized by cells and transfection efficiency. These new vectors show a remarkable capacity for mediating the internalization of pDNA with minimum cytotoxicity, being this effect positively correlated with the CH2– content present in the hydrophobic corona. Gene expression in MSCs, a cell type with relevancy in the regenerative medicine clinical context, is also enhanced using the new vectors but, in this case, the higher efficiency is shown by the vectors containing the smallest hydrophobic chain s[78] The use of dendrimers as gene transfection agents and drug-delivery devices have been extensively studied by Broeren *et al* & Boas *et al*[79, 80]. Kukowska *et al* reported that intravenous

administration of G9 PAMAM dendrimer-complexed pCF1CAT plasmid could result in high level of gene expression in the lung tissues of rats. It enhances the transfection efficiency and expression pattern of dendrimer[81]. Tziveleka *et al* prepared Fourth generation poly (propylene imine) dendrimer, completely or partially functionalized with guanidinium groups. The remaining toxic primary amino groups of the dendrimers were reacted with propylene oxide affording the corresponding hydroxylated derivatives. These guanidinylated dendrimers were interacted with plasmid DNA affording the corresponding dendriplexes.Their transfection efficiency was assessed employing HEK 293 and COS-7 cell lines.Guanidinylation of the parent dendrimer resulted to significant enhancement of its transfection efficiency, this enhancement being dependent on the number of guanidinium groups per dendrimer[82]. Caminade et al investicated that the water solubility of phosphorus-containing dendrimers was mainly due to the presence of hydrophilic end groups, which bear either positive or negative charges. These dendrimers can be used as in vitro DNA transfecting agents or in vivo anti-prion agents[83]. Wada et al have reported that galactose-α-cyclodextrines conjugations with degree of substitution of the galactose moiety was the most preferential carrier among the prepared series because it provided good gene transfer activity in vitro with no cytotoxicity. Consequently, the potential use of Gal-α-CDE conjugate (DSG 4) could be expected as a non-viral vector to deliver gene and these data may be useful for design of α-cyclodextrins and galactose conjugates with other non-viral vectors[84] . PAMAM dendrimers functionalized with α-cyclodextrin showed luciferase gene expression about 100 times higher than for unfunctionalized PAMAM or for non-covalent mixtures of PAMAM and α-cyclodextrin [85]. Luganini *et al* reported the ability of two peptide dendrimers, SB105 and SB105_ A10, to directly and almost completely inhibit human cytomegalovirus (HCMV) replication in both primary fibroblasts and endothelial cells; the agents were also found to inhibit murine CMV replication, whereas they were not able to inhibit adenovirus or vesicular stomatitis virus[86]. Dufes *et al* indicated different generations of PPI dendrimers as transfection agents, gene efficiently expressed in the liver rather than other organs. Furthermore, they demonstrated that intravenous administration of a gene medicine and G3 PPI dendrimer complex could result in intratumoral transgene expression and regression of the established tumours in all the experimental animals [87]

Dendrimers as imaging agents:-

The first in vivo diagnostic imaging applications using dendrimer-based MRI contrast agents were demonstrated in the early 1990s by Lauterbur and colleagues [88]. Bakalova *et al* compared

quantum dots coated with non-cross linked amino-functionalized polyamidoamine (PAMAM) dendrimers, quantum dots encapsulated in cross linked carboxyl-functionalized PAMAM dendrimers, and silica-shelled amino-functionalized quantum dots. A multimodal fluorescent and paramagnetic quantum dot probe was also developed and analyzed. The probes were applied intravenously in anesthetized animals for visualization of brain vasculature using two-photon excited fluorescent microscopy and visualization of tumours using fluorescent IVIS® imaging (Caliper Life Sciences, Hopkinton, MA) and magnetic resonance imaging[89]. Gadolinium is an FDA-approved contrast agent for MRI which provides greater contrast between normal tissue and abnormal tissue in the brain and body. It is safer than the iodine type contrast used in CT scans and also non-radioactive and is rapidly cleared by kidneys[90]. G3 (n = 16), G5 (n = 64) of Gd(III)DTPA-terminated poly(propylene imine) dendrimers and Gd(III)DTPA complex [G0 (n = 10)] reference were synthesized and investigated for relaxivities and concentration detection limits [91].

Other applications:-

Losada et al investicated ferrocene-containing dendrimers as mediators in amperometric biosensors is described. The steady-state amperometric response of carbon paste electrodes containing these dendritic relay systems and glucose oxidase is investigated as a function of the glucose concentration and the applied potential. The results show that these sensors respond rapidly to the addition of glucose[92].

Xia et al developed a simple convergent procedure for the preparation of triphenylamine dendrons containing an alkene at the center, which can be coupled in a single step to give dendrimers that contain truxene for the core without any protection–deprotection chemistry. These conjugated dendrimers exhibit similar absorption and emission behaviours in solutions and in thin films, which are indicative of the high isolation effect of well-organized three-dimensional dendrimers. They also have high fluorescence quantum yields and high glass transition temperatures, which indicate that these dendrimers are candidates for the application in OLED as light emitting materials[93]. Agashe *et al* studies the bio-distribution pattern of the fifth generation of poly (propylene imine) dendrimer (PPI-5.0G)-based carbohydrate (mannose and lactose)-coated glycodendrimers in mice so as to explore the potential of these systems as drug carriers[94]. Perumal et al carried out synthesis of enone core based dendrimers with carbazole as surface group. All the synthesized dendrimers showed excellent antioxidant behaviour with commercially available 1, 1-diphenyl-2-picryl hydrazyl (DPPH) [95].

CONCLUSIONS:

The high level of control over the dendritic architecture makes dendrimers ideal carriers in drug delivery applications. Small organic drug molecules with diverse structures have been success fully formulated with dendrimers, either through physical association with the dendrimer surface and/or interior, or through chemical conjugation between drug and dendrimer surface. Easily controllable features of dendrimers such as their size, shape, branching length, their surface functionality allow to modify the dendrimers as per the requirements, makes these compounds ideal carrier in many of the applications. Boosting of commercial applications of dendrimer technology will provide strength for its usefulness in coming years. This review is based on several research reports and their outcomes have been cited here in a concise manner. We hope this article will contribute to the new researchers for further investigations.

REFERENCES:

1. BhuleierE, Wehner W, Vogtle F. Cascade- and nonskid-chain-like syntheses of molecular cavity topologies. Synthesis 1978; 155–158.
2. Tomalia, DA., Baker H, Dewald JR., Hall M, Kallos G, Martin S, Roeck J, Ryder J, Smith P. A new class of polymers: Starburst- dendritic macromolecules. Polym J 1985; 17: 117–132.
3. Babu VR, Mallikarjun V, Nikhat S, Srikanth G. Dendrimers: A New Carrier System for Drug Delivery. Int J Pharma Applied Sci 2010; 1: 1-10.
4. Padilla O,Ihre H, Gagne L, Fréchet J, Szoka F. Polyester dendritic systems for drug delivery applications: in vitro and in vivo evaluation. Bioconjug Chem 2002; 13: 453–461.
5. Tomalia DA. Starburst dendrimers-nanoscopic macromolecules according to dendritic rules and principles. Macromol Symp 1996; 101: 243–255.
6. Hawker CJ, Fréchet JM. Preparation of polymers with controlled molecular architecture. A new convergent approach to dendritic macromolecules. J Am Chem Soc 1990; 112: 7638–7647.
7. Klajnert B, Bryszewska M. Dendrimers: properties and applications. Acta biochimica polonica 2001; 48:199–208.
8. Nanjwade B, Bechra H, Derkar G, Manvi F, Nanjwade V. Dendrimers: Emerging polymers for drug-delivery systems. Eur J Pharma Sci 2009; 38:185–196.

9. Nishiyama N, Kataoka K. Current state, achievements and future pros-pects of polymeric micelles as nanocarriers for drug and gene delivery. Pharmacol Ther 2006; 112: 630–648.
10. Nanjwade B, Bechra H, Derkar G, Manvi F, Nanjwade V. Dendrimers: Emerging polymers for drug-delivery systems. Eur J Pharma Sci 2009; 38: 185–196.
11. Na C, YiyunX, Yang T, Xiaomin W, Zhenwei L, Dendrimers as potential drug carriers, Part II: Prolonged delivery of ketoprofen by in vitro and in vivo studies. Eur J Pharma Sci 2006; 41: 670–674.
12. Sadler K, Tam J. Peptide dendrimers: applications and synthesis. J Biotechnol 2002; 90: 195-229.
13. Antoni P, Hed Y, Nordberg A, Nystrom D, Holst H, Hult A, Angew, M. Bifunctional Dendrimers: From Robust Synthesis and Accelerated One-Pot Post functionalization Strategy to Potential Applications. Int Ed 2006; 48: 2126-2130.
14. Babu VR, Mallikarjun V, Nikhat S, Srikanth G. Dendrimers: A New Carrier System for Drug Delivery. Int J Pharma Applied Sci 2010; 1: 1-10.
15. Jackson JL, Chanz HD, Booy FP, Drake BJ, Tomalia DA, Bauer BJ, Amis EJ, and Visualization of dendrimer molecules by transmission electron (TEM): staining methods and Cryo-TEM of vitrified solutions. Macromolecules 1998; 31: 6259–6265.
16. Svenson S, Tomali DA. Dendrimers in biomedical applications-reflections on the field. Adv Drug Deliv Rev 2005; 57: 2106–2129.
17. Cheng Y, Zhenhua X, Minglu M, Tongwen X. Dendrimers as drug carriers: applications in different routes of drug administration. J Pharm Sci 2008; 97: 123–143.
18. Ramaswamy C, Sakthivel T, Wilderspin A, Florence A. Dendriplexes and their characterization. Int J Pharm 2003; 254: 17-21.
19. Sakthivel T, Toth I, Florence A. Synthesis and physicochemical properties of lipophilic polyamide dendrimers. Pharm Res 1998; 15: 776-782.
20. Percec V, Cho WD, Mosier PE, Ungar G, Yeardley DJP. Structural analysis of cylindrical and spherical supramolecular dendrimers quantifies the concept of monodendron shape control by generation number. J Am Chem Soc 1998; 120: 11061–11070.
21. Bieniar C, Dendrimers: applications to pharmaceutical and medicinal chemistry. In: Encyclopaedia of Pharmaceutical Technology. Marcel Dekker, New York. 1998; 55–89.

22. Patri A, Majoros I, Baker J. Dendritic polymer macromolecular carriers for drug delivery. Curr Opin Chem Biol 2002; 6: 466-471.
23. Morgenroth F, Reuther E,Mullen K, Polyphenylene Dendrimers: From Three-Dimensional to Two-Dimensional Structures Angewandte Chemie. Int Ed 1997; 36: 631-634.
24. Nanjwade, Hiren B. Dendrimers: Emerging polymers for drug-delivery systems. Eur J Pharm Sci. 2009; 38: 185-196.
25. Lorenz K, Hölter D, Stühn B, Mülhaupt R, Frey H. Amesogen-functionize carbosilane dendrimer: a dendritic liquid crystalline polymer. Adv Mater 1996; 8: 414–416.
26. Boiko N, Zhu X, Bobrovsky A, Shibaev V. First photosensitive liquid crystalline dendrimer: synthesis, phase behaviour, and photochemical properties. Chem Mater 2001; 13: 1447–1452.
27. Betley TA, Hessler JA, Mecke A, Banaszak Holl MM, Orr BG, Uppuluri S, Tomalia DA, Baker JR. Tapping mode atomic force microscopy investigation of poly(amidoamine) core–shell tecto(dendrimers) using carbon nanoprobes. Langmuir 2002; 18: 3127–3133.
28. Ritzén A, Frejd T. Synthesis of a chiral dendrimer based on poly functional amino acids. Chem Commun 1999; 207–208.
29. Dvornic PR, de Leuze-Jallouli AM, Owen MJ, Perz SV. Radially layered poly(amidoamine-organosilicon) dendrimers. Macromolecules 2000; 33: 53–66.
30. Jain NK, Khopade AJ. Dendrimers as potential delivery systems for bioactive. Advances in controlled and novel drug delivery. CBS Publishers & Distributors, New Delhi; 2001: 361–380.
31. Colinger M. Biological applications of dendrimers. Curr Opin Chem Biol 2002; 6: 742–748.
32. Crespo L, Sanclimens G, Pons M, Giralt E, Royo M, Albericio F. Peptide and amide bond-containing dendrimers. Chem Rev 2005; 105: 1663–1681.
33. Bruckdorfer T, Marder O, Albericio F, From production of peptides in milligram amounts for research to multi-tons quantities for drugs of the future. Curr Pharm Biotechnol 2004; 5: 29–43.
34. Turnbull WB, Stoddart JF. Design and synthesis of glycodendrimers. Rev Mol Biotechnol 2002; 90: 231–255.

35. Tomalia DA. Birth of a new macromolecular architecture: dendrimers as quantized building blocks for nanoscale synthetic polymer chemistry. Prog Polym Sci 2005; 30: 294–324.
36. Barbara K, Maria B. Review Dendrimers: properties and applications**.** Acta Biochimica Polonica. 2001; 48: 199–205.
37. Lee CC, MacKay JA, Fréchet JMJ, Szoka FC. Designing dendrimers for biological applications. Nat. Biotechnol.2005; 23: 1517-1526.
38. Crampton H, Simane E. Dendrimers as drug delivery vehicles: non-covalent interactions of bioactive compounds with dendrimers. Polymer int 2007; 56 : 489-496.
39. Barbara K, Maria B. Dendrimers properties and applications. Acta biochimica polonica 2001; 48: 199-208.
40. Jevprasesphant R, Penny J, Attwood D, McKeown NB, DEmanuele A. Engineering of dendrimer surface to enhance transepithelial transport and reduce cytotoxicity. Pharm Res 2003; 20: 1543–1550.
41. Naha P, Davoren M, Lyng F, Byrne H. Reactive oxygen species (ROS) induced cytokine production and cytotoxicity of PAMAM dendrimers in J774A.1 cells. Toxicology and Applied Pharmacology 2010; 246: 91–99.
42. Esfand R, Tomalia D. A Polyamidoamine Dendrimer-Capped Mesoporous Silica Nanosphere-Based Gene Transfection Reagent. Drug Discov Today 2001; 6 : 427–436.
43. Svenson S, Chauhan AS. Dendrimers for enhanced drug solubilisation. Nanomedicine 2008; 3: 679–702.
44. Cheng Y, Xu T. The effect of dendrimers on the pharmacodynamic and pharmacokinetic behaviours of non-covalently or covalently attached drugs. Eur J Med Chem 2008; 43: 2291–2297.
45. Asthana A, Jain N. Dendritic systems in drug delivery applications. Expert Opin Drug Deliv 2007; 4 : 495–512.
46. Devarakonda B, Hill R, De Villiers, M. The effect of PAMAM dendrimer generation size and surface functional group on the aqueous solubility of nifedipine.Int. J. Pharm. 2004; 284: 133–140.
47. Cheng Y, Xu T. Dendrimers as Potential Drug Carriers. Part I. Solubilization of Non-Steroidal Anti-Inflammatory Drugs in the Presence of Polyamidoamine Dendrimers. J Med Chem 2005; 40: 1188–1192.

48. Chauhan A, Jain N, Diwan P, opade A. oly(amidoamine) (PAMAM) dendritic nanostructures for controlled site specific delivery of acidic anti-inflammatory active ingredient. AAPS PharmSciTech. 2005; 12: 575–583.
49. Beezer A, King A, Martin I, Mitchel J, Twyman L, Wain C. Dendrimers as potential drug carriers; encapsulation of acidic hydrophobes within water soluble PAMAM derivative Tetrahedron, 2003; 59 : 3873–3880.
50. Liang O, Lifang M, Bo J, Yanhua L, Dongsheng H, Li G. Synthesis of novel dendrimers having aspartate grafts and their ability to enhance the aqueous solubility of model drugs, Eur J Medi Che 2010; 45: 2705-2711.
51. Bhadra D, Bhadra S, Jain N. PEGylated lysine based copolymeric dendritic micelles for Solubilization and delivery of artemether J Pharm Pharm Sci 2005; 8: 467–482.
52. Gupta U, Agashe H, Jain N**.** Polypropylene Imine Dendrimer Mediated Solubility Enhancement: Effect of pH and Functional Groups of Hydrophobes. J Pharm Pharm Sci 2007; 10: 358–367.
53. Namazi H, Adell M. Dendrimer of citric acid and poly(ethylene glycol) as the new drug –delivery agent. Biomaterials 2005; 26: 1175–1183.
54. Jain N, Gupta U. Application of dendrimer-drug complexation in the enhancement of drug solubility and bioavailability. Expert Opin Drug Metab Toxicol 2008; 4: 1035-1052
55. Gupta U, Agashe H, Asthana A, Jain N. dendrimer: novel polymeric nanoarchitectures for solubility enhancement. Biomacromolecules. 2006; 7: 649–658.
56. Cheng Y, Xu Z, Ma M, Xu T. Dendrimers as drug carriers: Applications in different routes of drug administration. J Pharm Sci 2008; 97: 123–143.
57. Na M, Yiyun C, Tongwen X, Yang D, Xiaomin W, Zhenwei, L. Dendrimers as potential drug carriers. Part II. Prolonged delivery of ketoprofen by in vitro and in vivo studies. Eur J Medi Che 2006; 41: 670–674.
58. Sweet M, Kolhatkar R, Ray A, Ghandehari H. Transepithelial transport of PEGylated anionic poly (amidoamine) dendrimers: Implications for oral drug delivery. J Control Release 2009; 38:8-85.
59. Bhadra D. Bhadra, S, Jain N. PEGylated peptide-based dendritic nanoparticulate systems for delivery of artemether. J Drug Del Sci Tech 2005; 15: 65–73.
60. Yang H, Kao W. Dendrimers for pharmaceutical and biomedical applications. Journal of biomaterials science. Polymer edition 2006; 17: 3-19.

61. Chauhan A, Jain A. Dendrimer mediated transdermal delivery; enhanced bioavailability of indomethacin. . J Control Release 2003; 96: 537-540.
62. Cheng Y, Man N, Xu T, Fu R, Wang X, Wang X, Wen L. Transdermal delivery of nonsteroidal anti-inflammatory drugs mediated by polyamidoamine(PAMAM) dendrimers. J Pharm Sci 2007; 96: 595–602.
63. Chauhan AS, Sridevi S, Chalasani KB, Jain AK, Jain SK, Jain NK, Diwan PV. Dendrimer-mediated transdermal delivery: enhanced bioavailability of indomethacin. J Control Release 2003; 90: 335–343.
64. Bai S, Thomas C, Ahsan F. Dendrimers as a carrier for pulmonary delivery of enoxaparin, a low molecular weight heparin. J Pharm Sci 2007, 96, 2090–2106.
65. Thomas TP, Patri AK, Myc A, Myaing MT, Ye JY, Morris TB, Baker JR. In vitro targeting of synthesized antibody-conjugated dendrimer nanoparticles. Biomacromolecules 2004; 5: 2269–2274.
66. Okuda T, Kawakami S, Akimoto N, Niidome, T.;Yamashita, F.; Hashida, M. PEGylated lysine dendrimers for tumor-selective targeting after intravenous injection in tumor-bearing mice. . J Control Release 2006; 116: 330–336.
67. Choi Y, Thomas T, Kotlyar A., Islam MT, Baker JR. Synthesis and functional evaluation of DNA-assembled polyamidoamine dendrimer clusters for cancer cell-specific targeting. Chem Biol 2005; 12: 35–43.
68. Kojima C, Kono K, Maruyama K, Takagishi T. Synthesis of polyamidoamine dendrimers having poly(ethylene glycol) grafts and their ability to encapsulate anticancer drugs. Bioconjug Chem 2007; 11: 910–917.
69. Shuai X, Merdan T, Schaper A, Xi F, Kissel T. Core-cross-linked polymeric micelles as paclitaxel carriers. Bioconjug Chem 2004; 15: 441–448.
70. Shim W, Kim S, Choi E, Park H, Kim J, Lee D. Novel pH sensitive block copolymer micelles for solvent free drug loading. Macromol Biosci 2006; 6:179–186.
71. Lee H, Zeng F, Dunne M, Allen C. Methoxy poly(ethylene glycol)-blockpoly(d-valerolactone) copolymer micelles for formulation of hydrophobic drugs. Biomacromolecules 2005; 6: 3119–3128.
72. Yusa S, Fukuda K, Yamamoto T, Ishihara K, Morishima Y. Synthesis of well defined amphiphilic block copolymers having phospholipids polymer sequences as a novel biocompatible polymer micelle reagent. Biomacromolecules 2005; 6: 663–670.

73. Ooya T, Lee J, Park K. Hydrotropic dendrimers of generations 4 and 5: synthesis, characterization, and hydrotropic solubilization of paclitaxel. Bioconjug Chem. 2004; 15: 1221–1229.
74. Tang S, Martinez L, Sharma A. Synthesis and characterization of water-soluble and photostable L-DOPA dendrimers. Org Lett 2006; 8: 4421– 4424.
75. Patri AK, Majoros IJ, Baker JR. Dendritic polymer macromolecular carriers for drug delivery. Curr Opin Chem Biol 2002; 6: 466–471.
76. Asthana A, Chauhan AS, Diwan PV, Jain NK. Poly(amidoamine) (pamam) dendritic nanostructures for controlled site specific delivery of acidic anti-inflammatory active ingredient. AAPS PharmSciTech. 2005: 6.
77. Balogh L, Swanson DR, Tomalia DA, Hagnauer G, McManus A. Dendrimer–silver complexes and nanocomposites as antimicrobial agents. Nano Lett 2001; 1:18–21.
78. Santos J, Oliveira H, Pandita D, Rodrigues J, Pêgo A, Granja, P, Tomás, H. Functionalization of poly(amidoamine) dendrimers with hydrophobic chains for improved gene delivery in mesenchymal stem cells. J Control Release 2010; 144: 55–64.
79. Broeren M, van Dongen J, Pittelkow M, Christensen J, van Genderen M, Meijer E. Multivalency in the gas phase: the study of dendritic aggregates by mass spectrometry. Angew Chem Int Ed Engl 2004; 43: 3557–3562.
80. Boas U, Heegaard PMH. Dendrimers in drug research. Chem Soc Rev 2004; 33: 43–63.
81. Kukowska J, Chen C, Raczka E, Qunintana A, Rymaszewski M, Baker J. Intravascular and endobronchial DNA delivery to murine lung tissue using a novel, nonviral vector. Hum. Gene Ther 2000; 11:1385–1395.
82. Tziveleka L' Psarra A, Tsiourvas D, Paleos C, Synthesis and characterization of guanidinylated poly(propylene imine) dendrimers as gene transfection agents. J Control Release 2007; 117: 137-146.
83. Caminade A, Majoral J. Water-soluble phosphorus-containing dendrimers. Progress in Polymer Science. 2005; 30: 491-505.
84. Wada K, Arima H, sutsumi T, Hirayama F, Uekama K. Enhancing effects of galactosylated dendrimer/_-cyclodextrin conjugates on gene transfer efficiency. Biol Pharm Bull 2005; 28: 500–505.

85. Arima H, Kihara F, Hirayama F, Uekama K. Enhancement of gene expression by polyamidoamine dendrimer conjugates with and_α-cyclodextrins. Bioconjug Chem 2001; 12: 76–484.
86. Luganinia A, Giulianib A, Pirri G, Pizzuto L, Landolfo S, Gribaudo G. Peptide-derivatized dendrimers inhibit human cytomegalovirus infection by blocking virus binding to cell surface heparan sulphate. Antiviral Research 2010; 85: 532–540.
87. Dufes C, Keith WN, Bilsland A, Proutski I, Uchegbu IF, Schatzlein AG. Synthetic anticancer gene medicine exploits intrinsic antitumor activity of cationic vector to cure established tumors. Cancer Res. 2005; 65: 8079–8084.
88. Bakalova R, Zhelev Z, Aoki I, Kanno I. Designing quantum dot probes. Nat Photonics 2007; 1: 487–489.
89. Wiener E, Brechbiel M, Brothers H, Maginm R, Gansow O, Tomalia D, Lauterbur, P. Dendrimer-based metal chelates: a new class of magnetic resonance imaging contrast agents. Magn Reson Med. 1994; 31: 1–8.
90. Patri AK, Majoros IJ, Baker JR, Dendritic polymer macromolecular carriers for drug delivery. Curr Opin Chem Biol 2002; 6: 466–471.
91. Langereis S, Lussanet QG, van Genderen MHP, Meijer EW, Beets-Tan. Evaluation of Gd(III)DTPA-terminated poly(propylene imine) dendrimers as contrast agents for MR imaging. NMR Biomed 2006; 19: 133–141.
92. Losada J, Cuadrado I, Morán M, Casado C, Alonso B, M. Ferrocenyl silicon-based dendrimers as mediators in amperometric biosensors. Analytica Chimica Acta 1997; 338: 191-198.
93. Xia H, He J, Xu B, Wen S, Li Y, Tian WA. facile convergent procedure for the preparation of triphenylamine-based dendrimers with truxene cores. Tetrahedron 2008; 64: 5736-5742.
94. Agashe H, Babbar A, Jain S, Sharma R, Mishra A, Asthana A. Investigations on biodistribution of technetium-99m-labeled carbohydrate-coated poly(propylene imine) dendrimers. Nanomedicine: Nanotechnology, Biology and Medicine. 2007; 3:120-127.
95. Rajakumar P, Venkatesan N, Sekar K, Nagaraj S, Rengasamy R. Synthesis and antioxidant properties of enone core based dendrimers with carbazole as surface group. Eur J Medi Che 2010; 45: 1220–1224.