



International Journal of Biological & Pharmaceutical Research

Journal homepage: www.ijbpr.com

IJBPR

DENDRIMER: NOVEL DRUG DELIVERY SYSTEM A REVIEW

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ABSTRACT

Dendrimer as a drug delivery agent is a promising, safe and selective drug delivery method. It has highly selective nature for targeting the desired tissue is the most essential property. It is having promising future for the treatment of several disorders. And also it having other properties like very small in size, polyvalency, monodispersity, good stability makes it a good carrier for delivering drugs with precision and selectivity. Dendrimers are being used as drug delivery systems for many drugs like anticancer drugs, anti tubercular drugs, enhancing bioavailability of pilocarpine for ocular drug delivery. Dendrimer as a drug delivery system is based on the approach of injecting a nanoparticle (10-9) to the body, loaded with drug. The drug might be loaded on its encapsulated within the branches or terminal surface of a dendrimer. Dendrimers generally used to increased bioavailability especially sustained, controlled and targeted release of drug and there is reduction in the amount of drug and systemic toxicity while the therapeutic efficacy is increases. Thus present review focuses on the fundamentals of dendrimers and their use as drug delivery agents in treatment of various disorders.

Key Words: Dendrimers, Nanoparticle, Novel drug delivery, Targeting drug delivery.

INTRODUCTION

In 1978 Dendrimer chemistry was first introduced by Fritz Vogtle and coworkers. He synthesized the first "cascade molecules". In 1985, Donald A. Tomalia, synthesized the first family of dendrimers. The "dendrimer" word originated from two words, the Greek word *dendron*, meaning tree, and *meros*, meaning part. At the same time, Newkome's group independently reported synthesis of similar macromolecules. They called them "arborols" from the Latin word 'arbor' also meaning a tree. The term "A chemical or physiological process that occurs in successive stages" is also used, but 'dendrimer' is the best established one. Due to their multivalent and mono disperse character; dendrimers have stimulated wide interest in the field of chemistry and biology, especially in

applications like drug delivery, gene therapy and chemotherapy (Bai *et al.*, 2006)

Dendrimers are defined as synthetic macromolecules with a highly branched molecular structure that are synthesized in an algorithmic step-by-step fashion with every repeated sequence of reactions producing a higher generation (G) molecule that has a practically doubled molecular weight and a doubled (discrete) number of functional end-groups. Since 1985, numerous chemically different types of dendrimers have been developed, such as Tomalia's poly (amido amino) PAMAM-dendrimers, Newkome's arborols, Fréchet's poly ether dendrimers, Meijer and Mülhaupt's poly (propylene imine) PPI-dendrimers and Moore's phenylacetylene dendrimers. Because of their defined structure, narrow polydispersity, defined nanoscale size and the ease of modification of the end groups, dendrimers are considered interesting candidates for various functions in life sciences and medicinal chemistry. For example,

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their function as binding-and-release agents in drug and gene delivery has been investigated.

STRUCTURE OF A DENDRIMER

Dendrimers are built from a starting atom, such as nitrogen, to which carbon and other elements are added by a repeating series of chemical reactions that produce a spherical branching structure. As the process repeats, successive layers are added, and the sphere can be expanded to the size required by the investigator (Yiyun *et al.*, 2008). The result is a spherical macromolecular structure whose size is similar to albumin and haemoglobin, but smaller than such multimers as the gigantic IgM antibody.

Dendrimers are precisely defined, synthetic nanomaterials that are approximately 2-10 nanometers in diameter. They are hyperbranched 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 (Fig: 1).

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 (Padilla *et al.*, 2002).

Various components of dendrimer Structure (Newknom *et al.*, 1985)

Generations

From the centre of dendrimer i.e. core to the periphery, branching increases and a homostructural layer between a focal point or branching point is formed, number of focal point from centre to periphery is called as generation number. E.g.; G0 generation – initiator core has no focal points i.e. hydrogen substitutes G-5 generation-polypropylene imine (G-5 PPI) Intermediate form during the dendrimer synthesis has a half generation e.g. carboxylic- acid terminated PAMAM dendrimers.

Shell (Generation Space)

The dendrimer shell is the homo-structural spatial segment between the focal points, the “generation space”. The “outer shell” were the space between the last outer branching point and the surface. The “inner shells” are generally known as the dendrimer interior.

Pincer

Outer most shell has a many number of pincer created by last focal point before reaching to the surface. E.g. PPI and PAMAM dendrimer has many numbers of pincers half the number of surface groups.

End Group

It is also generally referred to as the “terminal group” or the “surface group” of the dendrimer. Dendrimers having amine end-groups are termed “amino-terminated dendrimers”.

ADVANTAGES OF DENDRIMER DRUG DELIVERY

A) This can produce Controlled and sustained release of drugs.

B) Can give medication to the affected part inside a patient's body directly (Nachiket *et al.*, 2010)

C) Solid tumours can be targeted by Dendrimer due to increased permeability, limited drainage in tumour vasculature which will lead to accumulation of macromolecules in tumour Boas U *et al.*, 2006) (enhanced permeation rate). In targeted delivery there is also reduction in amount of drug used (attaching site specific ligands at surface or magnetic guidance)¹⁴ and thus reduction in systemic toxicity

D) Therapeutic efficacy is increased, side effects is decreased: decreased clearance of drug via altered distribution of drug in tissues at site of localization and transportation due to controlled and sustained release of the drug

E) Preservation of drug activity: as drugs can be incorporated into the systems without any chemical response.

F) Drugs can be easily made to remain within layers of skin and not penetrate in systemic circulation

G) Bypassing the gastric medium and hence the eschewing the variation due to effect of gastric secretions.

H) Relatively high drug loading.

I) Limitations of other nanoparticles overcome; for example: overcoming limitations of liposomes like:

1. Efficiency of encapsulation is low.
2. In presence of blood components there is rapid leakage of water-soluble drug.
3. Poor storage stability.

CHARACTERIZATION OF DENDRITIC POLYMERS

The methods can be used for characterization of dendritic polymers.

Spectroscopy and spectrometry methods

Like Nuclear Magnetic Resonance (NMR), Infra-red (IR), Raman, Ultra-violet-visible (UV-VIS), Fluorescence, Chiral, Optical rotation, Circular dichroism (CD), X-ray diffraction and Mass spectrometry.

Scattering techniques

Like Small angle X-ray scattering (SAXS), small angle neutron scattering (SANS), and Laser light scattering (LLS)

Electrical techniques

Like Electron paramagnetic resonance (EPR), Electrochemistry, and Electrophoresis.

Size exclusion chromatography: (SEC) Microscopy

Like Transmission electron microscopy, scanning electron microscopy and atomic force microscopy.

Rheology, Physical properties

Like intrinsic viscosity, Dielectric spectroscopy (DS)

Miscellaneous

Like X-ray Photoelectron Spectroscopy (XPS), Differential Scanning Calorimetry (DSC), measurements of dipole moments, titrimetry etc.

SYNTHESIS OF DENDRIMER

Mainly two methods are used for the synthesis of dendrimers

Divergent growth method

In this method the growth of dendrimers originates from a core site. This approach involves assembling monomeric modules in a radial, branch-upon-branch motif according to certain dendritic rules and principles (Barbara K *et al.*, 2001). In this method, the core is reacted with two or more moles of reagent containing at least two protecting branching sites, followed by removal of the protecting groups. The subsequent liberated reactive sites lead to the first generation dendrimers. This process is repeated until the dendrimer of the described size is obtained.

Convergent growth method

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. When the growing wedges are large enough, several are attached to a suitable core to give a complete dendrimer. The advantages of convergent growth over divergent growth stem that only two simultaneous reactions are required for any generation-adding step (Manjoge A *et al.*, 2010)

OTHER APPROACHES

'Hypercores' and 'Branched Monomers' growth

This method involved the pre-assembly of oligomeric species which can be linked together to give dendrimers in fewer steps or higher yields.

Double Exponential growth

It is similar to a rapid growth technique for linear polymer. This approach allows the preparation of monomers for both divergent and convergent growth from a single starting. Then resulted two products are reacted to give an orthogonally protected trimer, which can be used to repeat the growth again.

TYPES OF DENDRIMERS

PAMAM Dendrimer

Poly (amidoamine) dendrimers (PAMAM) are synthesized by the divergent method starting from ethylenediamine or ammonia initiator core reagents. Products upto generation 10 (a molecular weight more than 9, 30,000 g/mol) have been obtained (when it compared to the molecular weight of human haemoglobin, is approximately 65,000 g/mol). PAMAM dendrimers are commercially available as methanol solutions. *Starburst dendrimers* are applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethyleneimine core. The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions (D. A. Tomalia *et al.*, 2005)

PAMAMOS Dendrimer

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

PPI Dendrimer

PPI-dendrimers are known as "Poly (Propylene Imine)" describing the propylamine spacer moieties in the oldest known dendrimer type developed initially by Vogtle. These dendrimers are basically poly-alkyl amines having primary amines as end groups. The dendrimer interior structure consists of numerous of tertiary tris-propylene amines. PPI dendrimers are commercially available up to G5, and it has found widespread applications in material science as well as in biology. As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM known for Poly (Propylene Amine), which closely resembles the PPI abbreviation. In addition, these dendrimers are also sometimes denoted "DAB-dendrimers" where DAB refers to the core structure, which is usually based on Diamino butane.

Tecto Dendrimer

These are composed of a core dendrimer and surrounded by dendrimers of several steps (each type design) to perform a function necessary for a smart therapeutic nanodevice. Different compounds perform different functions ranging from diseased cell recognition, diagnosis of disease state drug delivery, reporting location to reporting outcomes of therapy.

Multilingual Dendrimers

In multilingual dendrimers, the surface contains multiple copies of a particular functional group.

Chiral Dendrimers

The chirality in these dendrimers is based upon the construction of constitutionally different but chemically similar branches to chiral core.

Hybrid Dendrimers Linear Polymers

These are hybrids (block or graft polymers) of dendritic and linear polymers.

Amphiphilic Dendrimers

They are built with two isolated sites of chain end, one half is electron donating and the other half is electron withdrawing.

Micellar Dendrimers

These are unimolecular micelles of water soluble hyper branched polyphenylenes.

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 (Chai M *et al.*, 2001).

Frechet-Type Dendrimers

It is a more recent type of dendrimer developed by Hawker and Fréchet based on poly-benzyl ether hyper branched skeleton. These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalization, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media (Frechet J *et al.*, 2001).

SURFACE INTERACTIONS BETWEEN DRUGS AND DENDRIMER

The external surfaces of dendrimers have been considered as potential sites of interaction with drugs. Although the number of guest molecules are incorporated into a dendrimer may be dependent to a limited extent on the architecture of a dendrimer, the loading capacity may be dramatically increased by the formation of a complex with the large number of groups on the dendrimer surface. The number of surface groups available for drug interactions doubles with each increasing generation of dendrimer.

Electrostatic interaction between drug and Dendrimer

The presence of large numbers of ionisable groups on the surface of dendrimers provides an interesting opportunity for electrostatic attachment of numerous ionizable drugs, providing the resultant complex retains sufficient water solubility. For example electrostatic

interaction can occur between PAMAM dendrimers and nonsteroidal anti-inflammatory drug ibuprofen. Electrostatic interaction can occur between the carboxyl groups of this weakly acidic drug and the amine groups of the dendrimers. It has been estimated that approximately 40 ibuprofen molecules interact with G4 PAMAM dendrimer at pH 10.5 causing a considerable enhancement of drug solubility (Kabanov VA *et al.*, 1998).

Conjugation of drug to dendrimer

The covalent attachment of drugs to the surface groups of dendrimers through hydrolysable or biodegradable linkages offers the opportunity for a greater control over drug release. Yang and Lopina have conjugated penicillin V (XII) with both G2.5 and G3 PAMAM dendrimers through a PEG spacer via amide and ester bonds, respectively. The use of an amide linkage provided bond stability, whereas ester linkage of the drug to the dendrimer provided a means of controlling drug release via hydrolysis. The microbial activity of the penicillin released by ester hydrolysis of the PEG-PAMAM (G3) conjugate was approximately the same within 3% as that of non-modified Penicillin (Yang H *et al.*, 2003)

ENCAPSULATION OF DRUGS WITHIN THE DENDRITIC ARCHITECTURE

Dendritic architecture (open nature) has led several groups to investigate the possibility of encapsulating drug molecules within the branches of a dendrimer. This offers the potential of dendrimers to interact with labile or poorly soluble drugs, enhance drug stability, bioavailability and controlling its release. The nature of drug encapsulation within a dendrimer either may be simple physical entrapment or can involve non-bonding interactions with specific structures within the Dendrimer (Maciejewski M *et al.*, 1982).

Unimolecular micelles

Dendrimers consisting of a polar core and polar shell have been referred to as unimolecular micelles. For example synthesized a symmetrical, four directional saturated hydrocarbon cascade polymer containing 36 carboxylic acid moieties with a neopentyl core. It was shown that lipophilic probes were located within the lipophilic infrastructure of the dendritic structures and it was concluded that the polymers exist as single molecules capable of molecular inclusion and therefore act as unimolecular micelles (Newkome GR *et al.*, 1991)

PEGylated dendrimers

Poly (ethylene glycol) (PEG) has been used to modify dendrimers in the design of solubilizing and drug delivery systems. PEG is typically conjugated to the surface of a dendrimer to provide a hydrophilic shell around a hydrophobic dendritic core to form a

unimolecular micelle. Because of its high water solubility, biocompatibility and ability to modify the biodistribution of carriers so PEG is of particular interest in the design of dendrimer systems for pharmaceutical applications. Liu *et al.* pentanol based monomer was used to increase the flexibility and cavity size of the dendritic architecture by use of PEG (Liu M *et al.*, 2000)

Dendritic box

Jansen *et al.* described the synthesis of poly(propyleneimine) dendrimers based dendritic boxes. During the synthetic process, guest molecules could be entrapped within the cavities of the dendritic boxes with a dense surface shell preventing diffusion from the structures, even after prolonged heating, solvent extraction or sonication. Through end group modification with a bulky amino acid derivative to yield a dense and rigid chiral shell with solid-phase properties and a flexible core capable of entrapping molecules (Jansen *et al.*, 1995).

Cored dendrimers

Zimmerman and co-workers synthesized cored dendrimers that resemble hollow nanospheres, encapsulate substances made them candidates for delivery vehicles. Encapsulation was achieved by post synthetic modification of the dendritic architecture. The core unit in a typical dendrimer is essential as it interconnects the dendrons, or branches, of the structure. An alternative approach to maintaining the structural integrity of a dendrimer is to crosslink the peripheral surface groups (Wend Land *et al.*, 1999)

APPLICATION OF DENDRIMERS

Pharmaceutical application

Dendrimers in ocular drug delivery

Ideal ocular drug-delivery systems should be non-irritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable. Dendrimers provide unique solutions to complex 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 (Vandamme T *et al.*, 2005)

Dendrimers in pulmonary drug delivery

Dendrimers have been reported for pulmonary drug delivery of Enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40 %.

Dendrimers in transdermal drug delivery

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. PAMAM dendrimer complex with NSAIDs (e.g. Ketoprofen, Diflunisal) could be improving the drug permeation through the skin as penetration enhancers (Chang N *et al.*, 2007) Ketoprofen and Diflunisal were conjugated with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation. Chauhan *et al.* investigated enhanced bioavailability of PAMAM dendrimers by using indomethacin as the model drug in transdermal drug application (Chauhan AS *et al.*, 2003).

Dendrimers in oral drug delivery

Oral drug delivery studies using the human colon adenocarcinoma cell line, Caco-2, have indicated that low-generation PAMAM dendrimers cross cell membranes, presumably through a combination of two processes, i.e. paracellular transport and adsorptive endocytosis. Remarkably, the P-glycoprotein efflux transporter does not appear to affect dendrimers, therefore drug dendrimer complexes are able to bypass the efflux transporter (Emanuele D *et al.*, 2004) As increase in the concentration and generation, there was increase in the cytotoxicity and permeation of dendrimers.

Dendrimers in targeted drug delivery

Dendrimers have ideal properties which are useful in targeted drug-delivery system. One of the most effective cell specific targeting agents delivered by dendrimers is folic acid and methotrexate. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging respectively. 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 (Choi Y *et al.*, 2005).

Dendrimers in gene delivery

Dendrimer based transfection agents have become routine tools for many molecular and cell biologist's dendrimers are extensively used as non-viral vector for gene delivery. The use of dendrimers as gene transfection agents and drug-delivery devices have been extensively reviewed part (Broeren MAC *et al.*, 2004) Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

Dendrimer as solubility enhancer

Dendrimers have hydrophilic exteriors and hydrophilic interiors, which are responsible for its unimolecular micellar nature. They form covalent as well as non-covalent complexes with drug molecules and hydrophobes, which are responsible for its solubilisation behaviour (Jain NK *et al.*, 2008).

Cellular delivery using dendrimer carrier

Dendrimer-ibuprofen complexes entered the cells rapidly compared with pure drug (1 hr versus >3 hr),

suggesting that dendrimers can efficiently carry the complexes drug inside cells. PAMAM dendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake (Mohamad N *et al.*, 2006).

Dendrimers for controlled release drug delivery

The anticancer drugs adriamycin and methotrexate were encapsulated into PAMAM dendrimers (i.e. G=3 and 4) which had been modified with PEG monomethyl ether chains (i.e. 550 and 2000 Da respectively) attached to their surfaces. A similar construct involving PEG chains and PAMAM dendrimers was used to deliver the anticancer drug 5- fluorouracil. Encapsulation of 5- fluorouracil into G=4 PAMAM dendrimers modified with carboxymethyl PEG5000 surface chains revealed reasonable drug loading, a reduced release rate and reduced haemolytic toxicity compared with the non-PEGylated dendrimer.

A third-generation dendritic unimolecular micelle with indomethacin entrapped as model drug gives slow and sustained in vitro release, as compared to cellulose membrane control (Patri AK *et al.*, 2002). Controlled release of the Flurbiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM Dendrimers. The results found that PEG-

dendrimers conjugated with encapsulated drug and sustained release of methotrexate as compare to unencapsulated drug.

THERAPEUTIC APPLICATION

Dendrimers in photodynamic therapy

The photosensitizer 5-aminolevulinic acid has been attached to the surface of dendrimers and studied as an agent for PDT of tumorigenic keratinocytes (Snook S *et al.*, 2005). This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

Dendrimers for boron neutron capture therapy

Boron neutron capture therapy (BNCT) refers to the radiation generated from the capture reaction of low-energy thermal neutrons by ¹⁰B atoms, which contain approximately 20% natural boron, to yield particles and recoiling lithium-7 nuclei. This radiation energy has been used successfully for the selective destruction of tissue. Dendrimers are a very fascinating compound for use as boron carriers due to their well-defined structure and multivalency. The first example of boron containing PAMAM dendrimer was synthesized by Barth *et al.* (Barth RF *et al.*, 1994).

Table 1. Applications of Dendrimer

Types	Definition	Synthesis	Example	Applications
PAMAM Dendrimer	Poly (amidoamine) dendrimers possess amino groups on the surface.	Divergent	Dendritech TM (USA)	Material Science and Biomedicine Computer toners
PAMAMOS Dendrimer	Inverted unimolecular micelles consists of hydrophilic nucleophilic PAMAM interiors and hydrophobic organosilicon (OS) exteriors.	Convergent and Divergent	SARSOX	Nano-lithography, Electronics Photonics, Chemical catalysis, Precursor for honey comb like network preparations.
PPI dendrimer	Poly-alkyl amines having primary amines as end groups and its interior consists of numerous tertiary trispropylene amines.	Divergent	Asramol by DSM (Netherlands)	Material science and Biology
Tecto dendrimer	Composed of a core dendrimer with multiple dendrimers at its periphery	Divergent	Stratus® CS Acute Care TM, Starburst®, Mercapto	Diseased cell recognition, Diseased state drug delivery diagnosis Reporting location to outcome of therapy
Chiral dendrimers	Chirality is based on construction of Constitutionally different but chemically similar branches to a chiral core.	Convergent	Chiral dendrimers Derived from pentaerythritol.	Biomedical applications, Chiral catalyst
Hybrid dendrimers	Combination of dendritic and linear polymer in hybrid block or graft copolymer forms	Divergent	Hybrid dendritic linear polymer, Polysilsesquioxanes.	Biomedicals, Molecular electronics, Nanophotonics, Sensing.
Amphiphilic Dendrimers	Unsymmetrical globular dendrimers built with two	Divergent	Super Fect, Hydra amphiphile-s and	Structure-directing agent, use as polar part, cell and gene transfection.

	segregated sites of chain end.		bola-amphiphiles.	
Micellar Dendrimers	Unimolecular micelle structure of Water soluble hyperbranched polyphenylene	Divergent	Beclomethasone-dipropionate, NX-200, Magnevist®	Biological and medical applications, Drug delivery, Imaging agent.
Multiple antigen peptide dendrimers	Dendron-like molecular construct based upon a polylysine skeleton.	Convergent synthesis	Viva Gel	Used in vaccines and diagnostic research. Biological applications.
Frechettype Dendrimers	Dendrimers having carboxylic acid groups as surface groups and containing poly-benzyl ether hyper- branched skeleton.	Convergent synthesis	Frechet type dendronazides, Priostar TM	Drug carrier, Purifiers, Organic synthesis, detecting agent, drug delivery.
Liquid crystalline dendrimers	Consists of mesogenic monomers	Divergent	Polycanter liquid crystals, Mesogen functionalized carbosilane dendrimers	Science and Engineering.
Metallo Dendrimers	Dendrimers with incorporated metal atoms	Convergent	Zinc Porphyrin Dendrimers (M=Zn)	Sensing Catalytic applications, mimicbiomolecules, light harvesting, Biomarkers.
Peptide Dendrimers	Dendrimers having peptides on the surface and incorporating amino acids as branching or core units.	Convergent synthesis	Beta Casomorphin (human)	Drug delivery contrast agents for MRI, MRA, fluorogenic imaging and sero diagnosis, proteinmimetic.

Fig 1. Diagram showing the three main parts of a dendrimer, the core, end-groups, and subunits linking the two

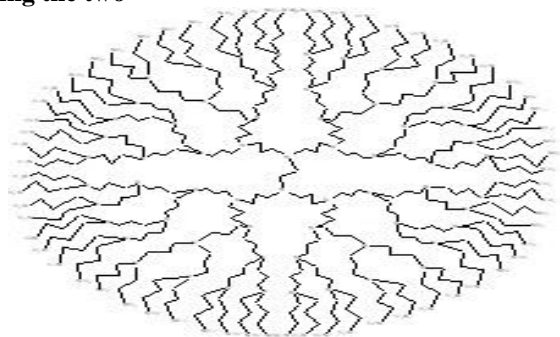


Fig 2. Divergent synthesis of dendrimer

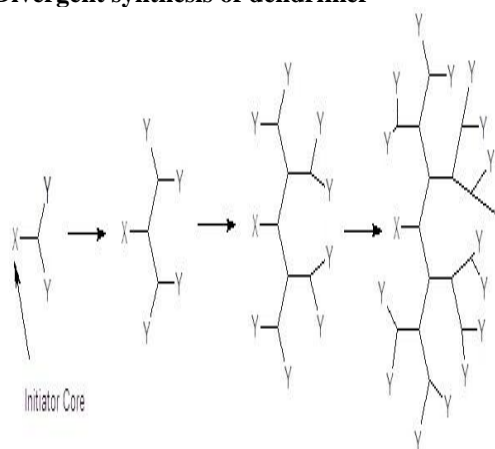


Fig 3. Convergent synthesis of dendrimers

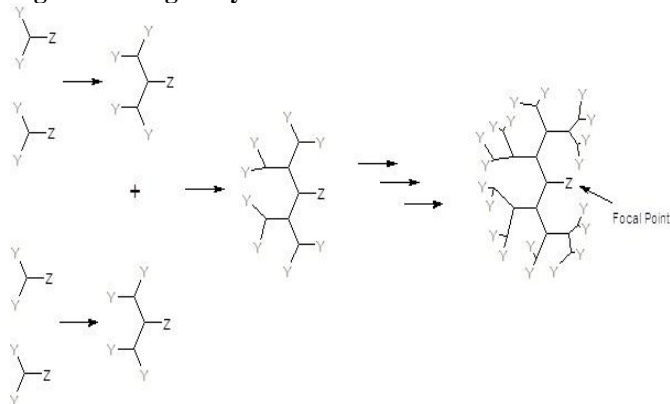


Fig 4. Dendritic box encapsulating guest molecules

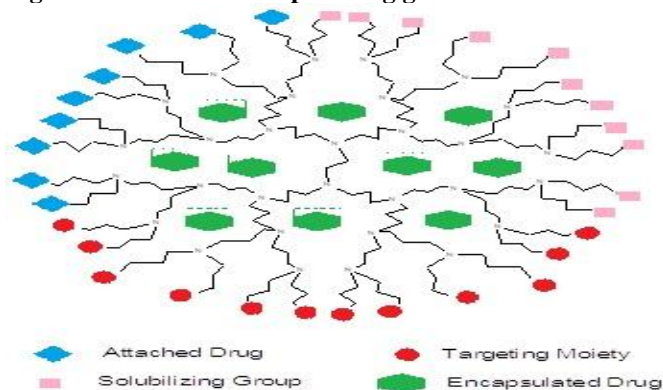
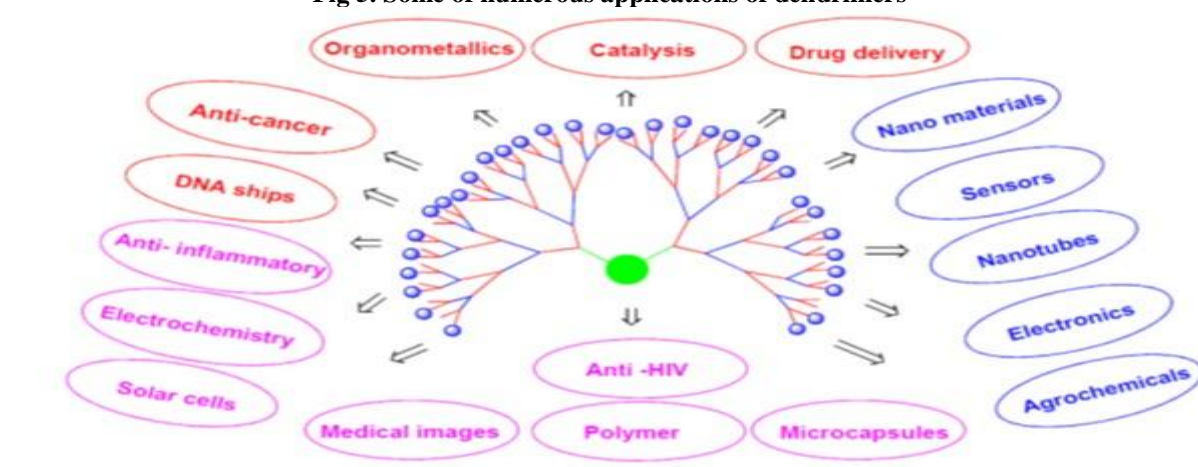


Fig 5. Some of numerous applications of dendrimers



DIAGNOSTIC APPLICATION

Dendrimers as molecular probes

Dendrimers are fascinating molecules to use as molecular probes because of their distinct morphology and unique characteristics. For example, the immobilization of sensor units on the surface of dendrimers is a very efficient way to generate an integrated molecular probe, because of their large surface area and high density of surface functionalities (Albrecht *et al.*, 2000).

Dendrimers as X-ray contrast agents

The X-ray machine is one of the fundamental diagnostic tools in medicine, and is applicable to numerous diseases. To obtain a high resolution X-ray image, several diseases or organs, such as arteriosclerotic vasculature, tumors, infarcts, kidneys or efferent urinary, require the use of an X-ray contrast agent. Dendrimers are currently under investigation as potential polymeric X-ray contrast agents. Krause and co-workers synthesized a number of potential dendritic X-ray contrast agents using various organo metallic complexes such as bismuth and tin (Schumann H *et al.*, 2003).

Dendrimers as MRI contrast agents

A number of research groups have explored the use of dendrimers as a new class of high molecular weight MRI contrast agents. Wiener and co-workers developed a series of Gd(III)-DTPA-based PAMAM dendrimers (Wiener *et al.*, 1994). To improve the pharmacokinetic properties of dendrimer contrast agents, introduction of target specific moieties to the dendritic MRI contrast

agents have been considered. He synthesized a folate conjugated Gd (III)-DTPA PAMAM dendrimer, which increased the longitudinal relaxation rate of tumor cells expressing the high affinity folate receptor.

Other applications

An alternative application of dendrimers that has gained some attention is based on nanostructures which can find use in environment friendly industrial processes. Dendrimers can encapsulate insoluble materials, such as metals, and transport them into a solvent within their interior. Cooper and co-workers synthesized fluorinated dendrimers which are soluble in supercritical CO₂ and can be used to extract strongly hydrophilic compounds from water into liquid CO₂. This may help develop technologies in which hazardous organic solvents are replaced by liquid CO₂. It has been a progressing field of research and at present all these industrial applications are under study.

CONCLUSION

Dendrimer are promising in solutions against poor solubility, bioavailability, permeability, diagnostic and many other fields of pharmaceutical applications thus, dendrimers holds a promising future in drug delivery. Also dendrimer having the unique properties of high degree of

branching, multi valency, globular architecture and well-defined molecular weight, thereby offering new scaffolds for drug delivery. Also as research progresses, newer applications of dendrimer will emerge and the future should witness an increasing numbers of commercialized dendrimer based drug delivery systems.

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