International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 6(2): March-April 2016

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Review Article……!!!

Received: 18-02-2016; Revised: 18-04-2016; Accepted: 19-04-2016

DENDRIMER: A SMART POLYMER FOR DRUG DELIVERY

Anurag Kumar*, Bhagyashree Parolkar, Abhijit Khobare, Vashisht Dhepe

Department of Pharmaceutics, NDMVP Samaj's College of Pharmacy, Nashik (MH) India

Keywords:

Dendrimer, PAMAM, Pincer, Immunogenicity, Hypercores

For Correspondence:

Anurag Kumar

Department of Pharmaceutics, NDMVP Samaj's College of Pharmacy, Nashik (MH) India

E-mail:

annuabhi2013@gmail.com

ABSTRACT

Dendrimers are hyper-branched, globular monodisperse, and 3D nanoscale synthetic polymers having well defined size, shape and definite molecular weight in drug delivery. These interesting features make them applicable in the field of nanotechnology, medicinal chemistry and pharmaceuticals for the delivery of various potent and non-potent drugs. But their actual utility in drug delivery can be assessed only after *in-vivo* studies. The review focuses on to the development, structure, synthesis, types and its applications. Different methods of dendrimer synthesis are available among which the review focused on convergent method, because it has easy to purify, and does not allow the formation of the high generation dendrimers. It also highlights the concept of click chemistry essential for dendrimer synthesis. Dendrimers also have tendency to target the particular site so these can be used for the long term treatment of the disease and for the diagnostic purpose. These are compatible with DNA, peptides and polyanions that make it more versatile in nature. The toxicity may be arises due to the cationic groups which can be minimized by the use of the fatty acid or PEG chains.

INTRODUCTION

Drug delivery is an important aspect of the formulation which on proper choice can enhance the bioavailability, solubility, target the action and reduce the toxicity.One of appropriate approach which can target to the above mentioned goals is dendrimers.

Dendrimers is originated from two Greek words i.e.-[2]

- DENDRON meaning TREE.
- MEROS meaning PART.

Dendrimers are hyper-branched, globular, monodispersed, three dimensional nanoscale synthetic polymers having very well defined size, shape and definite molecular weight. These are different from traditional polymers in that they have a multibranched three dimensional architecture with very low polydispersity and high functionality. It's a nanoparticle (10^{-9}) based drug delivery system.

Dendrimers is presently the internationally established term which is classically symmetric around the core and often adopt a globular 3D morphology. Dendrimers exhibit characteristic features of both molecularchemistry and polymer chemistry. Dendrons and dendrimers are commonly synthesized in a layer by layer fusion with high degree at control over the synthesis of each layer known as generation.

Basic Terms-

Dendrigrafts– These areclass of dendritic polymers like dendrimers that can be constructed with well-defined molecular structure i.e. being monodisperse. In contrast to dendrimer dendrigrafts are centered on a linear polymer chain to which branches consisting of co-polymer chain attached.

These co-polymer chains further modified with other co-polymer chains and so on giving hyper-branched motif built up a finite no. of combined polymers.

Dendrons- It is a term used about a dendritic wedge without a core the dendrimers can be prepared from assembling two or more dendrons. Dendrons are the very useful tool in the synthesis of dendrimers segment coupling strategy these dendrons have been used in the creation of numerous of dendrimers having different structure and functions.

Generations- It is common for all dendrimers designs and the hyper branching when going from the centre of the dendrimer towards the periphery resulting in homo structural layers between focal (branching points). The number of focal points when going from core towards the dendrimer surface is the generation.

Shell- Dendrimer shell number is homo structural spatial segment b/w the focal points the "generation space". The outer shell is the space b/w the last outer branching point and surface inner shell is generally referred as the dendrimer interior.

Pincer- in dendrimers, the outer shell consists of a varying no of the pincers created by the last focal points before reaching the dendrimer surface. In PPI & PAMAM dendrimers the no pincers is half of the surface groups.

End groups- It is referred as terminal group or surface group of dendrimers.

HISTORICAL DEVELOPMENT-

The First information about to the class of branched molecular were given at in 1974 in a publication written by a team of German chemist Fritz Vogtle and due to similarity in structure they were called "Octopus Molecules"[1]

Few years later in 1978 the same group described the synthesis of these compounds, this time giving them the name "Cascade Molecules" which were not the typical dendrimers.

The term dendrimer appeared for the first time in 1985 in the publication prepared by Donale Tomalia & Co- workers. This name refers to their tree like structure.

After one year same team describe the first of 2 currently known ways of synthesis of the compound i.e. divergent method. The method is based on the attachment of a new monomer to a multifunctional core. As a result of this research Tomalia obtained Polyamide Amine (PAMAM) Dendrimers. At the same time the group of Newkone synthesized the similar type of nanoparticle known as Arborols but this name was not adopted. In 1990, another approach introduced by the Jean Frechet known as Convergent synthesis.[11,12]

STRUCTURE

The structure of dendrimer possess 4 basic units- (Figure-1)

i) A central core moiety.

ii) Branching units which are radically attached with the central core. It possess important role for physical and chemical properties.

iii) Internal cavities.

iv) Terminal functional group/Surface group which are attached to the outermost series of branches.

PROPERTIES

A. These polymers can be synthesized with a well-defined molecular structure i.e. being monodisperse, unlike to linear polymers.

B. When the surface of the dendrimeric polymer is modified with small functional groups or PEG show non or low immunogenicity.

C. Numbers of terminal surface groups suitable for bi-conjugation of drugs signalling groups, targeting moieties.

D. When the mass of the dendrimer increases the intrinsic viscosity goes through a maximum up to the 4^{th} generation & than begins to decline.

E. Presence of many chain ends is responsible for high solubility and miscibility and reactivity to.

F. Dendrimers are being nontoxic, bio permeable, immunogenic, having ability to stay in a circulation for the time needed to have a clinical effect & targeting to specific structure.

G. Having ability to arrange excretion mode from body, as a function of the nanoscale diameter.

H. Surfaces may be designed with functional groups to resist transcellular epithelial or vascular bio permeability.

SYNTHESIS

Dendrimers can be considering 3 major part i.e. Core, inner cell, & outer cell. Synthetic procedures can correctly manage Size, and branches on the dendrimers. Mainly 4 methods are considered for the synthesis of dendrimers-

1) Divergent method
2) Convergent method
3) Double exponential and mixed growth.
4) Hypercores and Branched monomer growth.

1) Divergent Method- The method was introduced by the Tomalia. The method involves the assembling to form a multifunctional core which further extended outward by a sequence of the reactions.

Commonly Michael Addition reactions involves for the formation. The core is reacted with two or more moles of reagent containing at least two protecting branching sites followed by the removal of the protecting groups leads to the I^{ST} generation dendrimers. The process repeated until the dendrimer of the required size is obtained. [Fig-2]

PAMAMs/Starbust dendrimer were the first dendrimers which were synthesized by this method. The major disadvantage of this approach is that the incomplete growth and the side reactions lead to imperfect dendrimers.

2) Convergent method- Convergent dendrimer growth begins at what will end up begins at what will end up being the surface of the dendrimers & works inward by gradually linking surface units together with more. When wedges are large enough, several of them attach to the specific core to produce a complete dendrimer. [Fig.-2]

The method has various advantages like- a) Relatively easy to purify, b) Occurrence of the defects can be minimized, c) Does not allow the formation of the high generation dendrimer because stearic problems occurs in reaction of dendrons.

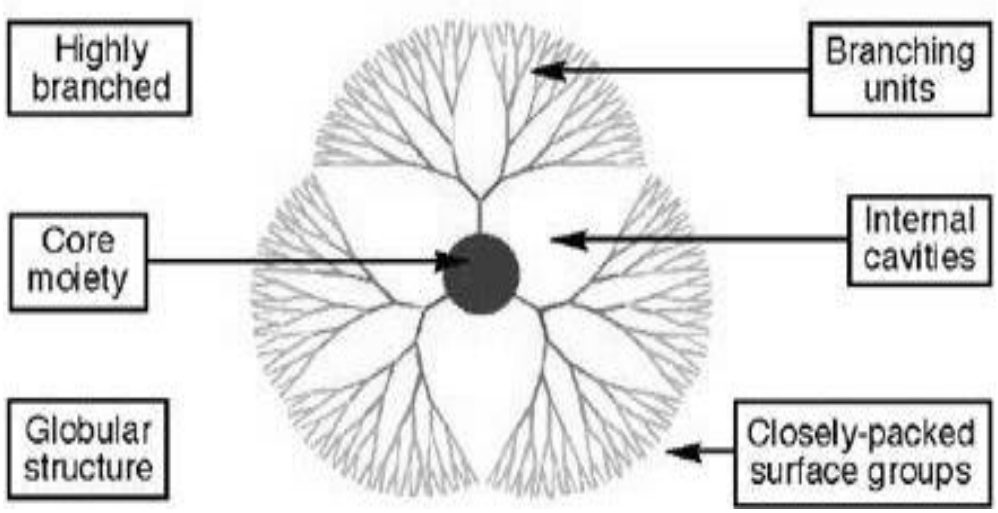

Figure-1- Structure of dendrimer

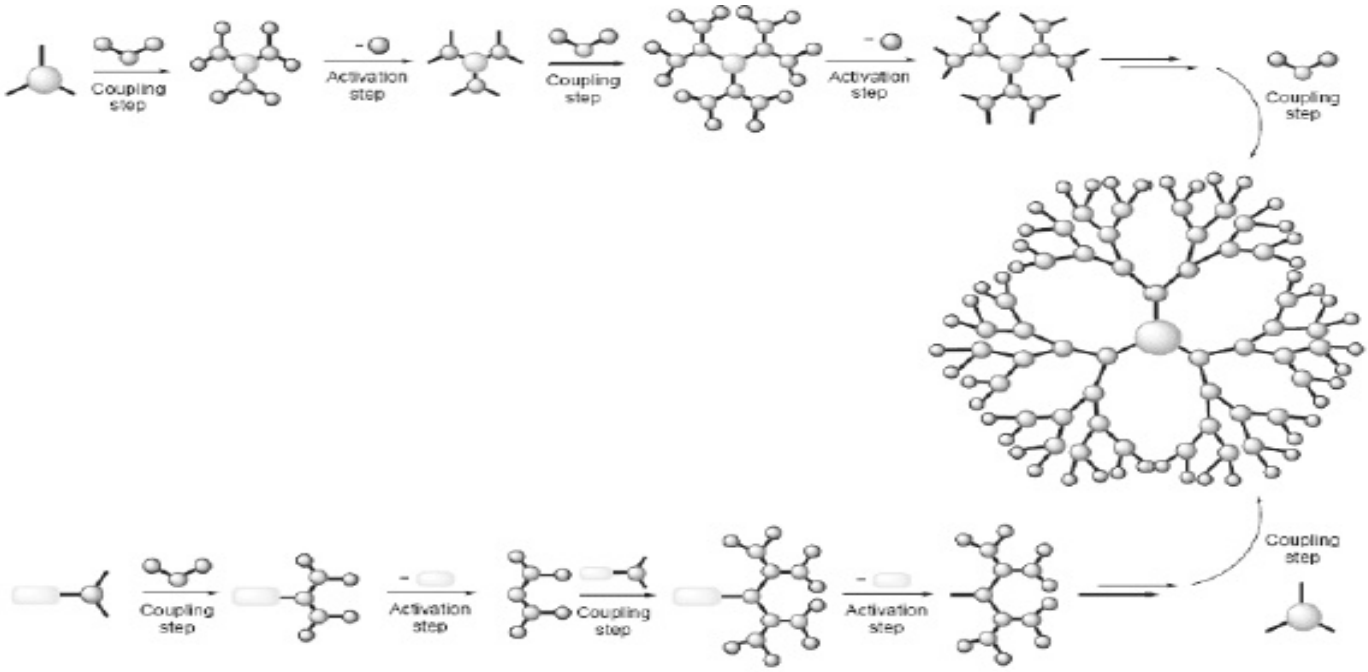

Figure-2. Synthesis of dendrimer Divergent (Top panel) & Convergent (Bottom pannel)

MOST SIGNIFICANT FEATURES OF CONVERGENT METHOD-

A) Its simplicity and great precision since growth steps generally involve only the coupling of the 2,dendrons to a monomer unit (rather than the ever increasing number of the coupling steps required in the divergent procedures) there by reducing the excess of the reagent needed to obtain high yields and facilitating purification at each step of growth.

B) Its Functional versatility enabling the preparation of the dendrons with differentiated & usually orthogonal functionalities, located respectively at the focal point & the chain ends of Dendron. Combining different dendrons to the dendrimer leads to the novel dendritic co-polymers with an unsymmetrical arrangement of the chain end functionalities or alternating building blocks that are not accessible by the divergent route.

C) Design versatility- as generic dendrons may be prepared to be used later as building blocks in conjunction with other reactive molecules or coupled to a multifunctional core to afford functional dendrimer, dendritic linear hybrids, dendronized polymers etc. This may be particularly significant advantages if the coupled reactive or core molecules are itself sensitive to the multiple steps of the interactive synthesis of the dendrimer.

Key criteria for a successful convergent synthesis-

A) Use of the high yielding reactions for all steps of synthesis.

B) Structural features that enable easy separation at various stages of growth.

C) Ability to incorporate varied functional groups at the focal point & at the chain ends of dendrons.

3) Double exponential and mixed growth-In this approach two products (Monomers for both divergent and convergent growth) are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again.

Strength of double exponential growth is more subtle than ability to build dendrimers in few steps.

4) Hypercores and Branched monomer growth- This method involves the preassembly of oligomeric species which can be linked together to give dendrimers in a fewer steps with high yield.

Click Chemistry

Dendrimers have been prepared via click chemistry. The concept of click chemistry was first introduced by K. Barry Sharoless of the Scripps Research institute in 2001 and describes chemistry modified to engender substance rapidly and consistent by combination of small units collectively.

It's not a solitary reaction but was intended to imitate nature that can also generate molecules by joining small molecules units. Use of click chemistry for the synthesis of dendrimers possesses various advantages- i) a modular. ii) Wide in scope. iii) Produce only harmless by-products IV) provide higher chemical yields. v) Stereospecific. vi)Physiologically stable.

A separate exothermic reaction makes a reactant *spring clouds*.

TYPES OF DENDRIMERS

A. PAMAM Dendrimer
B. PPI Dendrimer
C. Chiral Dendrimer
D. Multilingual Dendrimer
E. Tecto Dendrimer
F. Hybrid Dendrimer
G. Amphiphilic Dendrimer
H. Frechet-Type Dendrimer
I. Peptide Dendrimer
J. PAMAMOS Dendrimer

A) PAMAM Dendrimer- These are prepared by divergent method in which ammonia and ethylene-di-amine (EDA) is used as starting material. These are further identified by the shape i.e. spheroidal or ellipsoidal. The high solubility and reactivity of dendrimers Due to no. of functional end group and empty internal cavity. E.g. Dendritech ^{TM} (USA)

B) PPI/POPAM (Poly propylene imine/Amine)- the core structure of these types of polymer is based upon the Di-amino butane with poly alkyl amine as end groups and numerous tertiary propylene amines as interior. They are available up to 5^{th} generations. e.g. Astramol.

C) Chiral Dendrimer- Dendrimers construction is based upon the chirality around central core having constitutionality different but chemically similar branches. These are synthesized by the Convergent method.

D) **Multilingual Dendrimers-** These are the dendrimer having multiple copies of particular functional groups on their surface.

E) **Tecto Dendrimer-** These are made up of core dendrimer surrounded by either dendrimers, each of one will execute a specific function for therapeutic purpose as well as diagnose the disease state deliver the API to desire site.

F) **Hybrid dendrimers-** These dendrimers have features of both dendritic and linear polymer.

G) **Ampiphilic dendrimer-** it contain one half that is electron donating and another half is electron withdrawing groups.

H) **Peptide Dendrimers-** Peptide dendrimer are synthesized by convergent method where amino acid are branching or interior unit. They are used for diagnostic purpose and vaccine delivery.

I) **Frechet-type Dendrimer-** these are based on poly benzyl ether hyper branched skeleton. Carboxylic acid groups attachedon the surface of dendrimer which provides site for further functionalization & also improve solubility of dendrimers.

J) **PAMAMOS Dendrimer (poly-amido amine organosilicon)-** they are prepared by both divergent and convergent method. These are silicon containing commercial dendrimers which are …… unimolecular micelle and contain exterior hydrophobic organosilicon (OS) and interior hydrophilic nucleophilic polyamidoamine.

APPLICATIONS

Dendrimers are novel polymers having structural characteristics like nanoscopic size, spheroidal surface, high branching better encapsulation etc. due to their characteristic features dendritic polymers have broad no. of prospective applications in different fields. It includes the following-

A)Dendrimers in targeted drug delivery- the dendritic polymers provides the passive targeting of drug to solid tumours. This is due to their enhanced solubility and plasma circulation time. PAMAM dendrimer is used for Cisplatin delivery in which the drug form complex with exterior carboxylate group results in enhanced solubility compare to the free drug.

B)Dendrimers in genetic drug delivery- dendrimer based transferring agent can be used as carrier in gene therapy. In gene transformation the DNA is attached to a nanoparticle of inert solid which then exposed to cell nucleus. The use of dendrimer for transplantation was primarily reported by group of SZOKA and BAKER. Superfect^{TM} is a transferring reagent

which consists of activated dendrimers so as to carry large amount of genetic material then viruses. Various polyatomic compound such as PEI, polylysine, and cationic have been utilized as non-viral gene carrier.

C) Dendrimers as solubility enhancer- dendrimer having both hydrophilic and hydrophobic layer and act as a unimolecular micelles in nature dendrimer…. Nano CMC. With these properties they will improve solubility f poorly soluble drugs incorporated.

D) Dendrimers in TDDDS- recent advanced in TDDDS incorporate the use of dendrimers so has to increase penetration as well as diffusion across the skin. It provide controlled, steady administration of drug which extends the action of drug having short half-life during the reservoir of drug available in the delivery system and its controlled release which are efficient in treatment of acute and chronic rheumatoid and osteoarthritis, could be a recovering the drug penetration through the skin as diffusion enhancers.

E) Dendrimers in pulmonary drug delivery-Dendrimers have been reported forpulmonary drug delivery of Enoxaparin.G2 and G3 generation positively chargedPAMAM dendrimers increased the relative bioavailability of Enoxaparin by 40 %.

F) Dendrimers in photodynamic therapy- The photosensitizer 5-aminolevulinic acidhas been attached to the surface of dendrimers and studied as an agent forPDT of tumorigenic keratinocytes**50**. This cancer treatment involves the administration of a light- activated photosensitizing drug that selectively concentrates in diseased tissue.

G) 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. PAMAMdendrimers were surface engineered with lauryl chains to reduce toxicity and enhance cellular uptake.

H) Applications of Dendrimers in Waste Water Treatment:

Dendritic polymers are used in the purification of water contaminated by toxic metal ion, inorganic solute and organic solutes.

I) Dendrimers in Cosmetics: Dendrimers have a great contribution on cosmetics. Various cosmetics industry use dendrimers in the formulation. L'Oreal has a patent for using dendrimers in the production of cosmetics like mascara or nail polish. Unilever also have a patent for dendrimers in the production of formulation used in spray, gels and lotions.

CONCLUSION

Due to their absolute design dendrimers improved the physical and chemical properties. These have well defined size, shape, molecular weight, monodispersity and are unimolecular

miceller in nature. All these properties make dendrimer as smart choice for drug delivery with better drug loading and improved solubility and bioavailability of poorly soluble drugs. Despite of several advantages and utility dendrimers bring boom in field of the pharmaceuticals as a novel drug delivery approach but multistep synthesis of the dendrimer requires great effort and although further studies are required for better understanding of ADME (pharmacokinetic parameter) and in-vivo studies.

REFERENCES

1. Małgorzata K. Dendrimers-fascinating nanoparticles in the application in medicine. Chemik 2014; 68(2):141–150.
2. Malik A, Chaudhary S. et al. Dendrimer: A tool for drug delivery. Advance in biological research 2012; 6(4):165-169.
3. Baig T*,Nayak J, Dwivedi V. A review about Dendrimer synthesis, types, characterization and applications. International journal of pharmaceutical and bioscience 2015;4(1):44-59.
4. Trivedi V, Patel V, Bhimari B. et al. Dendrimer: Polymer of 21st century. International journal of research in pharmacy and chemistry 2012;1(2):1-21.
5. P* Priya, Mand S, Jeyapraghen R et al. Dendrimer: A novel polymer international journal of research in pharmacy and chemistry 2013;3(2):495-501.
6. Klajnert B. Bryszewska M. Dendrimers:Properties,and applications. Acta Biochimica Polonica 2001;48(1):199-208.
7. Patidar A Thakur DS Dendrimer A Potential Career For Drug Delivery 2011:4(2):1383-1389.
8. Doshi M.* Dendrimers and its application. International Journal of Pharmaceutical Sciences Review and Research 2011;7(2):104-111.
9. Tambe R.V.* Pakhre S.S. Jadhav G.M.etal. Dendrimers:A smart polymer. International Journal of Research and Reviews in Pharmacy and Applied science;2(3):513-528.
10. Abbasi E.Aval F.S. Akbarzadeh A. et al. Dendrimer: Synthesis, Application,& properties. Nanoscale Research Letters 2014;9(1):1-10.
11. II KM Synthesis of Dendrimer polymer. Microstructure design lab.
12. Boas U, Christensen JB, Heegard PMH. Dendrimers in medicine and biotechnology. The Royal society of chemistry 2006;81(103):152-154.
13. Haesnler j, Szoka FC. Polymeric gene delivery:Principles and applications. Bioconj. Chem 1993;4(5):372-379.
14. Teresa S, Barata, TI, Brocchini s,et al. Partially Glycosylated Dendrimers Block MD-2 and prevent TLR4-MD-2-LPS Complex Mediated Cytokinin Responses. PLoS Computational Biology 2011;7(6):1-12.
15. Csaba N, Garica-Fuentes M, Alonso MJ, The performance of nanocarriers for transmucosal drug delivery. Expert.opin.Drug Delivery 2006;3(4):463-478.
16. Vogtle F Weber E Octopus molecules. Angew Chem1974;12:814–816.
17. Buhleier E Wehner W Vogtle F Cascade-chain-like and nonskid-chain-like synthesis of molecular cavity topologies. 1978;(2):155–158.
18. Tomalia D A Baker H Dewald J A new class of polymers: starburst-dendritic macromolecules. Polym. J. 1985;17(1):117–132.
19. Holister P, Christina RV; Harper T, Dendrimers: Technology White Papers. Cientifica. 2010.
20. Gregory F, Kakkar AK Diels–Alder Click Chemistry in Designing Dendritic Macromolecules. Chem. Eur. J 2009;15(23):5630-5639.