INTERNATIONAL JOURNAL OF PHARMACEUTICS & DRUG ANALYSIS

VOL.6 ISSUE 4, 2018; 439 – 445 ; http://ijpda.com; ISSN: 2348-8948

Review Article

Dendrimers: A Platform for Novel Drug Delivery System

Gorkhe YS*, Pande VV, Autade RR

Sanjivani College Of Pharmaceutical Education And Research, Kopargaon, Ahmednagar, Maharashtra, India

Date Received: 17th March 2018; Date accepted: 29th March 2018; Date Published: 4th April 2018

Abstract

The review majorly based on four areas i.e., architecturing, synthesis, properties & applications of dendrimer. The dendrimers having unique architectural design of high degree of branching, multivalency, globular architecture and well defined molecular weight which distinguishesthis structure is unique and optimum nanocarriersin medical applications such as drug delivery, gene delivery, tumor therapy,diagnostic etc. It has some synthetic approaches lead to a dendritic architecture with properties complaisant to modification of shape, size, polarity,surface properties & internal structure.Nanoparticle drug delivery system is popular once are able to increase the stability and selectivity of therapeutic agents. The reticuloendothelial system (RES) uptake drug leakage, cytotoxicity, immunogenicity, hemolytic toxicity, hydrophobicity restrict the use of these nanostructure.And these problems are overcome by surface engineering the dendrimers such as, polyester dendrimer, citric acid dendrimer, argining dendrimer, glycol dendrimers, PEGlyated dendrimers, etc. The bioactive agents can be easily encapsulated in to the interior of the dendrimers and are chemically attached such as conjugated or physically absorbed onto the dendrimer surface,serving the desired properties of the carrier to the specific needs of active material and its therapeutic applications.In addition to supplying a multivalent backbone for drug attachment, dendrimers also provide access for various new polymer architectures that are potentially relevant to drug delivery applications.

Keywords: Dendrimer, Nanotechnology, Nanoparticle.

Abbreviations:

RES-Reticulo endothelial system; PEG-Polyethylene glycol; IgM-Immunoglobulin M; PPI-Polypropylene imine; PAMAM-Poly amidoamine; THF-Tetra hydro furan; HIV-Human immuno deficiency virus; NSAIDS-Non steroidal anti inflammatory; Caco-2-Colon Cancer cell lines; PEI-Polyethylene imine; DNA-Deoxyribo Nucleic Acid; FA-Folic acid; KB-KERATIN - Forming tumor cell line Hela

Introduction

One of the new class of polymeric material is dendrimers which are highly branched monodisperse macromolecules.Thestructure of these dendrimers has a great impact on their physical and chemical properties. Dendrimers are suitable for a wide range of biochemical and industrial applications due to result of unique behavior[1].FirtzVogtle and co-workers in 1978carried out very first successful attempt to create and design dendritic structures by using divergent synthesis, which are then followed by R.G.Denkewalter at allied corporation in 1978, in 1983 this perform by Donald Tomalia at Dow chemical's and George Newkome in 1985. Jean Frechet in 1990 introduces covergent synthetic approach [2].The world dendrimers comes from a Greek world that means the branches like tree[3]. The unique property of dendrimer is they have solubility in water [4].Dendrimers are highly branched synthetic polymer and these are consisting of monomer unit attached core, where a leading to monodisperse, tree like, star shaped (star burst) Cascade molecules i.e. Cauliflower [5]. The interior of dendrimersEndoreceptors binding groups are present (host guest is take place either in the interior) or in complexation chemistry on the periphery of the dendrimers endoreceptors groups are involved. Some of the properties of dendrimers are narrow polydispersity, Nano meter size range that can allow easier passage across biological barrier. Dendrimers is described as a macromolecule which is characte-

rized due to its dendritic and hyper branched 3D structure that offers a high degree of surface functionality and versatility. As Polymer of 21stcentury dendrimers are referred. They are ideal drug delivery system due to their feasible topology, functionality and dimension. Dendrimers having interest in field of chemistry gene therapy and chemotherapy, biology in application like drug delivery [6]. Hyper branched+ polymers are branched molecules synthesized under conditions where the resulting structures cannot be precisely defined [7]. Hyperbrached polymers are obtained by using one step polymerization reactions and exhibit properties that are very similar to those of perfect dendrimer analogues. Therefore, hyperbranched polymers are suitable alternative for dendritic nanocarrier system [8].

By using nitrogen as starting atom dendrimers are build to which carbon and other elements are added by a repeating series of chemical reactions which produce a spherical branching structure. Successive layers are added as the process going repeats and the sphere can be expanded to the size which is required by the investigator. The result is a spherical macromoleculecular structure that size is similar to hemoglobin and albumin but smaller than such multimers as the giganitic IgM antibody complex [9, 10].

Dendrimers consist of a series of chemical shells which built on small core molecule. Each shell consist of two chemicals, always in same order and is called generation. A central core which is either a single atom or atomic group has at least two identical chemical functions.

Branches emanating from the core constituted of repeat units having at least one branch junction, whose repetition is organized in a geometrical progression that result in series of radially concentric layers called generations .

Many terminal functional groups located in exterior of the macromolecules which is having important role in properties of dendrimers [11].

Generation–Center of dendrimers to forming branching like structure layer and this called homostructural layer and the point is also called branching point or focal point. This type of dendrimer content five foal point is nominated as fifth generation of dendrimers. This term known as G-5 dendrimer for eg. Fifth generation Polypropylene imine is abbreviated as "G5-PPI" G0" is donated a core part of dendrimer or presented "G0".

Shell- Homostructural spatial segment between the focal points is the shell of dendrimer. The space between the outermost last branch points is called outer shell. Dendrimer interior is inner shells.

Pincer- Various numbers of pincers are present on outer shell of dendrimer. In PAMAM and PPI dendrimers, the number of pincers is half the number of surface groups on it (because in these dendrimers the chain divides into two chains in each focal point)

End group – Dendrimers having amine end groups are called as amino terminated dendrimers [12].Ideally, dendrimer should be also non-immunogenic, non-toxic, and stable up tothe target, then cleavable into non-toxic small pieces to be easily excreted. Paul Ehrlich dreamed that dendrimer should be new magic "bullets" one century ago [13].

1.1 Structure of dendrimer

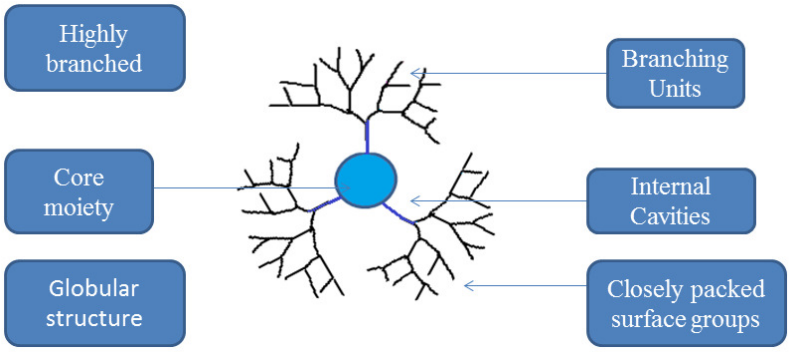

Fig.1 The structure of dendrimer.

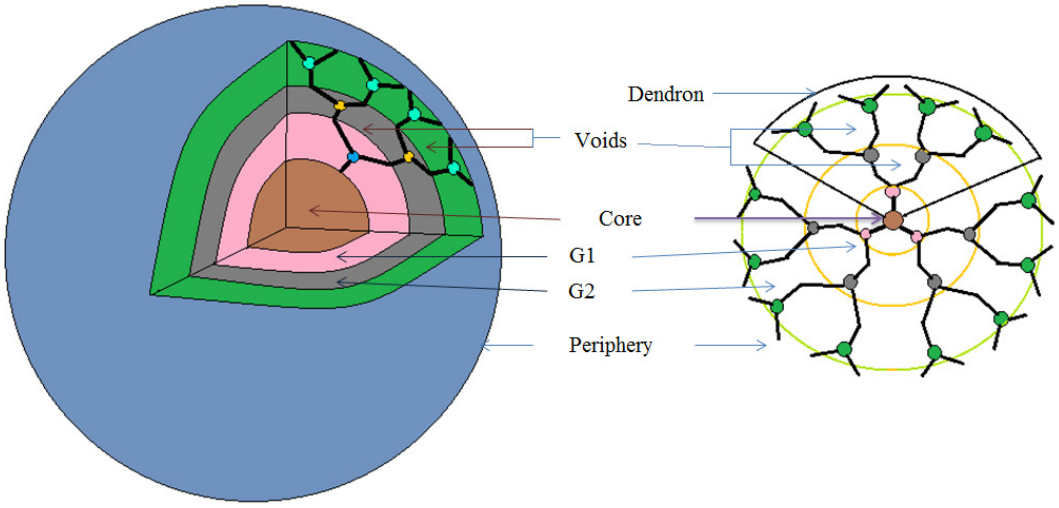

Fig.2 Core branches end group.

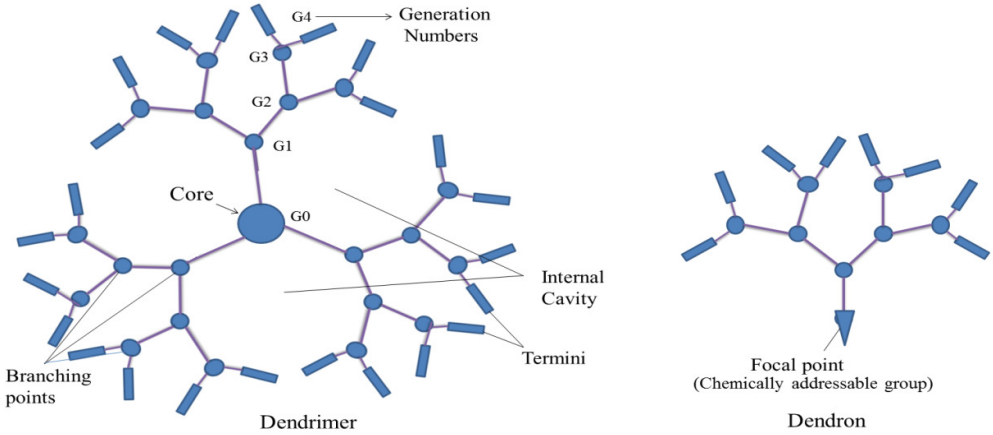

Figure 3: Structure of dendrimer with different generations (G=0 to G4) & structure of Dendron.

1.2 Ideal properties of dendritic polymer

- With small functional groups or polyethylene glycol (PEG) dendrimers surfaces are modifiedshow low – immunogenicity.
- Dendrimershaving ability to arrange excretion mode from body, as a function of nanoscale diameter.
- The interior void space of dendrimers areused to encapsulate small molecule drug, metals, or imaging moieties, reduces the drug toxicity &facilates controlled release [14].
- It is lesssusceptible for reticulum endothelium uptake due to its nanoscopic particle size range (1-100 nm).
- The physical encapsulation of drug into dendrimer for enhancement of water solubility several hydrophobic drug molecules such as, anti-cancer, anti-microbial,anti-inflammatory agent [15].
- Dendrimers chain ends which are responsible for miscibility, high reactivity and high solubility.
- The solubility of dendritic polyester is having higher solubility tetrahydrofuran (THF) as compare to analogues linear polyesters because of spherical shape of dendrimer and internal cavities [16].
- Dendrimer can adapt “native” or “denaturated” conformations depending up on polarity, ionic strength, Ph of solvent [17].

- High density and reactivity of functional groups which are present on the periphery of dendrimer prepared by a suspension oxidation reaction in an aqueous solution.
- Dendrimers having well defined globular structure, predictable molecule weight and monodispersitythatensure reproductive pharmacokinetic [18].
- It is having Ability to arrange excretion mode from body, as a function of nanoscale[19].
- It is use for specially used for enhancing half-life of drugs and reducing frequency of drug administration [20].
- It has anti- inflammatory activity, anti-HIV activity, anti- arthritis activity [21].
- It has host-guest entrapment properties[22].

1.3 General Properties of Dendrimer

1) Structure – Compact and Globular
2) Shape - Spherical
3) Architecture –Regular
4) Reactivity – High
5) Aqueous solubility– High
6) Nonpolar solubility –High
7) Crystallanity–Non crystalline and amorphous material lower glass temperature
8) Viscosity – Nonlinear relationship with molecular weight
9) Ionic conductivity – High
10) Compressibility –Low [23].

2. Mechanism of Drug Delivery throughDendrimers

There are broadly two mechanisms for drug dendrimer.

2.1 In vivo degradation of drug dendrimers is first one covalent bonding which depends up on presence of suitable enzymes or the environment is capable of cleaving the bond.

2.2 Second mechanism is carried out by releasing the drug due to changes in physical environment such as, pH, temperature this mechanism is independent of external factors and take place in the cavities of core24].

3. Application of dendrimers in drug delivery system

3.1 Dendrimers in ocular drug delivery

Ideal ocular drug delivery system should be have properties such as nonirritating,serial,isotonic,biocompatible, does not run out from the eye and biodegradable. For ocular drug delivery dendrimerprovideunique solution to complex delivery problem. By using PAMAM dendrimers with the carboxyl hydroxyl surface grouprecent research efforts for improving residence time of pilocarpine in the eye was increased. In case of synthesize hydrogel that increase the volume in aqueous solution and these are more similar to living tissue by the addition of PEG groups to the dendrimer, these hydro gel having application in cartilage production for sealing the ophthalmic injuries. In ocular drug molecules hydrogel is composed of PEGlyated-dendrimers are attach to the dendrimer and out to the eyeefficient drug delivery is carried [25].

3.2 Dendrimer in transdermal drug delivery

The delivery of drug through skin to achieve systemic effect of drug is called as transdermal drug delivery. In this case the drug transport through dermaland epidermaltissue of skin for local therapeutic effect [26].Because of adverse reactions such as GI and renal side effects when they are given by oral route the clinical use of NSAIDs is limited. These bad effects is overcomes by transdermal drug delivery and also maintain therapeutic blood level for longer period of time. Due to the of barrier function of skin transdermal delivery suffers poor rate of transcutaneous delivery Bioactive drug consisting hydrophobic moieties and having low solubility characteristic therefore the dendrimers are the good choice in this field[27].

3.3 Dendrimers in pulmonary drug delivery

In this case the polyamidoamine (PAMAM) dendrimers having absorption enhancing effect with the generations i.e., G0-G3 and concentrations 0.1% -1.0% (w/v) on the pulmonary absorption of peptide and protein drugs where studied in animal model rats [28].

3.4 Dendrimers in oral drug delivery

Human colon adenocarcinoma cell line (Caco-2) used in oral drug delivery studies have indicated that low generation PAMAM dendrimer cross cell membranes, by the combination of two process, i.e. Paracellular transport adsorption endocytosis [29].

3.5 Dendrimer in gene delivery

For many molecular and cell biologist dendrimers –based on transfection agents have become routine tools are extensively used as non-viral vector for gene delivery. The dendrimers are use

as gene transfection agent and drug delivery devices have been extensively reviewed part various polyatomic compound i.e. PEI, Polylysine and cationic have been utilized as non-viral gene carrier [30]. Transfection agent (superfect) consisting of activated dendrimer it is commercially available. As compare to liposomes the superfect DNA complex are characterized by high stability and provide more efficient transport of DNA in to nucleus [31].

3.6 Dendrimer for targeted drug delivery

Dendrimers having unique structural features and properties make them ideally suited for both wide range of biomedical applications and platform for biometric chemistry [32]. Dendrimers possess some ideal properties which are useful in targeted drug delivery system. Compared to the systemic delivery the targeted drug delivery of chemotherapeutics to tumor cell reduces the side effects. For increasing specific delivery multifunctional dendritic artichecture allows conjugation of both drug and target moieties such as, folic acid monoclonal antibodies, and peptides to the dendrimers periphery. The poor water solubility of many drugs, especially anti-cancer drugs, leads to the application of intravenous administration route in clinical trial [33]. By surface modification of dendrimer the site specific delivery of drug obtaining by using various targeting moieties such as Folic acid (FA), peptides , monoclonal antibodies and sugar groups. By engineering the branching units the passive targeting obtains and surface groups of dendrimer. Conjugated FA to G5 PAMAM dendrimer for targeted delivery of methotrexate and observed receptor mediated drug delivery that demonstrated high specificity for KB cells overexpressing folate receptors and showed slower drug release [34].

3.7 Dendrimer for controlled released drug delivery

In this case drug delivery involved encapsulation of 5-flurourcil into PAMAM dendrimer (G=4) and it is modified with carboxy methyl PEG 5000 surface chain revealed reasonable drug loading due to this reduce rate and reduce hemolytic toxicity . Controlled released of drug Flurbiprofen obtain by the formation of complex with the amines terminated generation PAMAM Dendrimers [35].

3.8 Dendrimers as solubility enhancer

Because of both hydrophobic and hydrophilic layer dendrimers are unimolecular micellar in nature. Hydrophilic layer leads to formation of the core and hydrophilic layers forms the outer surface. Dendrimers don't have critical micelle concentration. Because of these properties dendrimers enhance the solubility of poorly soluble drug by forming covalent non-covalent complexes with the drug molecules and hydrophobe [36].

3.9 Dendrimers as drug delivery carriers in cancer therapy

Dendrimer can be used as unimolecular micelles and dendritic "boxes" for the monovalent encapsulation of drug molecules. For example, DNAwascomplexed with PAMAM dendrimers for gene delivery applications and dendrimers core incorporated with hydrophobic drugs and dye molecules. Advantage of using dendritic unimolecular micelles than conventional polymeric micelles is that the micellar structure is maintained at all concentrations because the hydrophobic segments are covalently connected. A general drawback in that it is difficult to control the release of molecules from the dendrimer core. In some conditions the encapsulated drug is not well retained and the molecules are released relatively rapidly and another approach to the development of dendrimers as anticancer drug carriers is to exploit their well-defined multivalency for covalent attachment of drug molecules tothedendrimer periphery. By varying the generation number of the dendrimer the drug loading can be tuned. And release of the drug can be controlled by incorporating degradablelinkages between the drug and dendrimer. For example, encapsulation ofanticancer drug cisplatin within PAMAM dendrimers gave conjugates that exhibited slower release, higher accumulation in solid tumors, and lower toxicity compared to free cisplatin [37]. The internal cavities of dendrimers a characteristics of the structure are in most cases hydrophobic and allow the interaction with poorly soluble drug [38].

Conclusion

The Dendrimers are nanoparticles which are one of the systemic approaches towards the effective and specific drug delivery. It is novel and smart material for drug delivery. Its various features such as shape, density, branching, globular architecture and their surface functionality make ideal carrier in biomedical application. Poor solubility, permeability and bioavailability problems are

overcome by use of dendrimers. Targeting a drug to required area is possible because of this smart drug delivery.

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