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An Overall Review on Preparation and Applications of Dendrimers

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***Abstract*: Dendrimers are a new class of polymeric substances, which are highly branched, monodisperse, and artificial macromolecules dendrimers having a well-defined, shape, size, molecular weight and monodispersity. In1978, vogtle was first introduced chemistry of dendrimer. In 1980 Donald tomalia and coworkers discovered highly branched polymers called dendrimers dendrimers has a wide range of application in pharmaceutical field, as diagnostic substitute as blood substituent, as solubility enhancer now-a-days dendrimers are main nanoparticles which are applied to drug delivery systems. The review is focused on method of preparation and applications of dendrimers. Nano formulations are mainly based on dendrimers which enhances low solubility drugs, arrives to target tissues, drugs bioavailability and controlled release. Dendrimers are macromolecular structures , the drugs can be ensnare in the infra molecular cavity of the dendrimers and which are conjugated to their surface biological properties such as polyvalence, self-assembling, electrostatic interactions, chemical stability, low cytoxicity and solubility . These diverse characteristics make dendrimers a good choice in the medical field this review covers types and applications.**

***Keywords*: Polymeric substances, diagnostic substitute, solubility enhancers, nanoparticles, target tissues, bioavailability.**

1. Introduction

The first idea of branched molecules was stated by Flory in 1941[1]. The first paper regarding dendritic structure was published by vogtle and coworkers, this discovery was confirmed by denkewatter et. Alin in 1981 tomalia et. Al. In1983and newkome et. Al in 1985 [2]. Dendrimers are synthetic polymers characterised by branched repeating units that merge from a focal point and posess a large number of exposed anionic, neutral or cationic terminal functionalities on the surface, which leads to hydrophilic and hydrophobic compounds [3]. They are nanometric molecules which are radially symmetric, globular, monodispersed and homogenous [4]. The properties of dendrimers are different in to conventional polymers due to their size, dendrimers are used in Nano medicine research [5] dendrimers are nano sized radially symmetric molecules with well-defined homogenous and monodisperse structure consisting of tree like arms or branches [6], these hyper branched molecules were first discovered by fritz vogtle in1978 by Donald tomalia and coworkers in the early 1980s [7]. Dendrimers might also be called cascade molecule, but this term is not as much established as dendrimers. [8] Dendrimers is only an architectural motif and not a compound. [9] Polyionic dendrimers do not have a persistent shape and may undergo changes in size, shape, and flexibility as a function of increasing generations [10], dendrimers have gained abroad range of applications in supra molecular chemistry. The advantages of these well-defined materials make them the newest class of macromolecular nano scale delivery devices dendritic macromolecules tend to linearly increase in diameter and adopt a more globular shape with increasing dendrimers generation. [11] The benefits of many drugs cannot be exploited because of their poor solubility, toxicity or stability problems, the use of dendrimers as carriers of these compounds can solve these problems through clinical a [12] Moreover, the structural versatility of dendrimers gives special qualities in the context using them as ideal carrier for many active drug molecules [13]. Mainly, many recent studies involving DDS using dendrimers have been in the field of neoplastic diseases dendrimers also studied as DDS in other therapeutic fields anti-inflammatory, antiviral, antibiotic therapies and in cardiovascular diseases [14]. Due to their significance in the field of medicine dendrimers have been studied intensively in the past few years [15].

2. Structure

The structure of dendrimers molecular begins with a central atom begins with a central atom or group of atoms labelled as the core from this central structure, the branches of other atoms called Dendron's grow through a variety of chemical reactions [16].There continues to be a debate about the exact structure of dendrimers in particular whether they are fully extended with maximum density at the surface or whether the end group's fold back into a densely packed interior [17].the structure of some dendrimers repeat units, for example, the 1,3diphenylacetylene unit developed by Moore [18]. Dendrimers are a new class of polymeric belongings their chemistry is one of the most

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attractive and hastily growing areas of new chemistry. The unique structure of dendrimers provides special opportunities for host guest chemistry and is specially equipped to engage in multivalent interactions [19]. At the same time, one the first proposed applications of dendrimers was a container compound where in small substrates are bond with in the internal voids of the dendrimers [20].

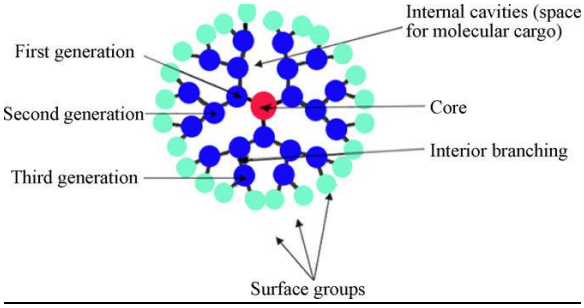

Fig. 1. Structure of Dendrimer

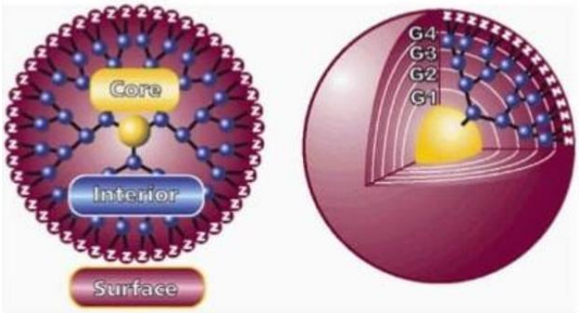

Fig. 2. 3D Structure of Dendrimer

3. Types of Dendrimer

1. PAMAM Dendrimer
2. PAMAMOS dendrimers
3. PPI dendrimers
4. TECTO dendrimer
5. Multilingual dendrimers
6. Chiral dendrimers
7. Hybrid dendrimers linear polymers
8. Amphiphilic dendrimers
9. Micellar dendrimers
10. Multiple antigen peptide dendrimers
11. FRECHET-type dendrimers

A variety of dendrimers have been developed and since the 1980s, but the ones derived polyamidoamine [PAMAM] are Undeniably the most employed they are hydrophilic biocompatible non immunogenic systems which favors their use in drug delivery the core of PAMAM is most Commonly ethylene diamine although more hydrophobic molecules Their branching unit are based on methyl acrylate and ethylene diamine and they have amine and carboxyl terminated groups. They referred to them as a cascade of molecules.

4. Dendrimer Synthesis

- Divergent
- Convergent Approaches
- Combined Divergent and Convergent Approaches

In the divergent method the molecules grows radially from a core by the sequential addition of layers of monomers each layer constitute a new generation. The number of surface groups multiplies according to functionalities in each monomer ramification. [21] Every step of the reaction is fully completed before the addition of a new generation to avoid defects in the branches, it reasonably fast synthesis which allows the preparation of large dendrimers [22]. By this method, the higher the generation, greater the chances are of having branching defects, since the presence of bulky branches creates difficulties in the coupling of new ones [23]. In an opposite way from the divergent synthesis, dendrimers can also be synthesized starting from the surface using a convergent approach. The growth of the molecule starts from the end of the chain beginning by integrating the various branching points with other monomers constitute dendrimers [24]. In contrast to divergent growth, this method permits easier purification due to bigger differences between the final products and the initial reagents. Some advantages include higher mono-dispersity for low generations and fewer branches defects. In this strategy, the final generation is predetermined, necessitating the synthesis of branches of a variety of requisite sizes beforehand for each generation [25].

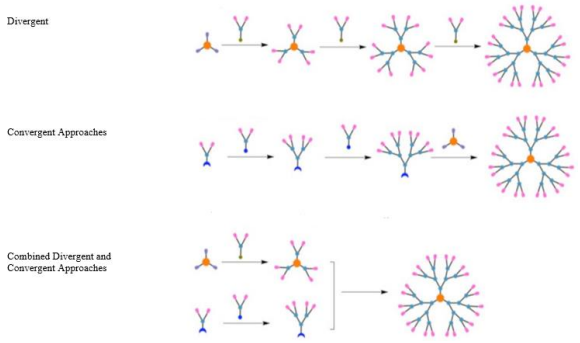

Fig. 3.

5. Applications

Today dendrimers have several medicinal and practical applications.

6. Dendrimers in Biomedical Field

Dendritic polymers have advantage in biomedical applications these dendritic polymers are analogous to protein enzymes and viruses, and are easily functionalized. Dendrimers and other molecules can either be attached to the periphery or can be encapsulated in their interior voids modern medicine uses a variety of this material as potential blood substitutes, e.g. polyamidoamine dendrimers [26].

7. Anticancer Drugs

Perhaps the most promising potential of dendrimers is in their possibility to perform controlled and specified drug delivery one of the most fundamental problems that are set toward modern medicine is to improve pharmacokinetic properties of drugs for cancer. [27] Unique pathophysiological traits of tumours such as extensive angiogenesis resulting in hyper

vascularization, the increased permeability of tumour vasculature and limited lymphatic drainage enable passive targeting, and as a result, selective accumulation of macromolecules in tumour tissue. This phenomenon is known as enhanced permeation and retention. [28, 29]. The drug dendrimer conjugates show high solubility, reduced systemic toxicity, and selective accumulation in solid tumors. Different strategies have been proposed to enclose within the dendrimer structure drug molecules, genetic material, targeting agents, and dyes by conjugation, encapsulation and complexation.

8. Dendrimers in Drug Delivery

The utilization of these highly branched molecules as molecular containers [30]. Host guest properties of dendritic polymers are currently under scientific investigation and have gained crucial position in the field of Supramolecular chemistry.

9. Transdermal Drug Delivery

Clinical use of NSAIDs is limited due to adverse reactions such as GI side effects and renal side effects when given orally. Transdermal delivery suffers poor rates of transcutaneous delivery due to barrier function of the skin. Bio active drugs having hydrophobic moieties in their structure and low water solubility, dendrimers are a good choice in the field of efficient delivery system [31].

10. Blood Substitution

Dendrimers are used as blood substitutes. Their steric bulk surrounding a hememimetic centre significantly slows degradation compared to free heme, and prevents the cytotoxicity exhibited by free heme [32].

11. Oral Drug Delivery

Oral route most widely used route strong acid and enzyme present in stomach causes degradation of drug. Dendrimer interior is hollow so it provides good site for drug entrapment. This entrapment increases solubility as well as stability of drug [33, 34].

E.g. PAMAM dendrimers conjugated with the folic acid and fluorescein isothiocyanate for targeting the tumor cells and imaging. Dendrimer provide protective layer reduces the effect of acid and enzyme.

12. Ocular Drug Delivery

The intraocular bioavailability of topically applied drugs is extremely poor. Ideal ocular drug delivery systems should be nonirritating, sterile, isotonic, biocompatible, does not run out from the eye and biodegradable. Dendrimers provide unique solutions to complex delivery problems for ocular drug delivery.

E.g. Recent research efforts for improving residence time of pilocarpine in the eye was increased by using PAMAM dendrimers with carboxylic or hydroxyl surface groups [35].

13. Pulmonary Drug Delivery

Dendrimers have been reported for pulmonary drug delivery of enoxaparin. G2 and G3 generation positively charged PAMAM dendrimers were reported to increase the relative bioavailability of Enoxapariby 40 % [36].

14. Transdermal Drug Delivery

Dendrimers have found applications in transdermal drug Delivery systems.

Dendrimers has been found to improve solubility and plasma circulation time via transdermal formulations and to deliver drugs efficiently.

E.g. PAMAM dendrimer complex with (e.g. ketoprofen) diflunisal were conjugated with G5 PAMAM dendrimer and showed 3.4 and 3.2 times higher permeation.

2. Controlled release of the flubiprofen could be achieved by formation of complex with amine terminated generation 4 (G4) PAMAM dendrimers [37].

15. Antineoplastic Drug Delivery

The star polymer gave the most promising results. In addition to improving drug properties such as solubility and plasma circulation time polymeric carriers can also facilitate the passive targeting of drugs to solid tumors. The cytotoxicity of doxorubicin was successful taken up by several cancer cell lines [38, 39].

16. Gene Transfection

Dendrimers can act as vectors, in gene therapy. PAMAM dendrimers have been tested as genetic material carriers. Numerous reports have been published describing the use of amino-terminated PAMAM or ppias non-viral gene transfer agents, enhancing the transfection of DNA by endocytosis and into cell nucleus [40, 41].

17. X-ray Contrast Agents

Dendrimers are under investigation as potential dendritic x-ray contrast agents using various organo metallic complexes such as bismuth and tin are used to obtain a high resolution x-ray image, kidneys or efferent urinary [42, 43].

18. MRI Contrast Agents

Introduction of target specific moiety to the dendritic MRI contrast agents, to improve the pharmacokinetic properties of dendrimer agent. [44-46].

19. Dendrimers in Drug Therapy

Cancer is an Is an abnormal proliferation of cells caused by numerous changes Factors leading to an imbalance between cell proliferation and apoptosis and eventually evolving into distant site invasive cells, causing significant morbidity and mortality. [47] Chemotherapy is linked with important toxicity nephro, hepato, hemato. And cardiotoxicity. [48]. The carrier capacity of dendrimers offers an advantage and constituents an important strategy in cancer therapy, dendrimers having the role

of useful ligands in transporting the drug molecule to tumor tissue through biological compartments [49].

20. Conclusion

Dendrimers are nanoparticles used for the synthesis of drugs, which are macromolecular dendrimers are characterized by individual features that make them hopeful candidate for a lot of applications. Dendrimers increases stability of drug polyethylene glycol [PEG] having less cytoxicity, dendrimers possess many applications due to their structural versatility. They can be used in different fields like photodynamic therapy immunology, bio pharmacy; the multi-step synthesis still requires great effort. Physicochemical properties are important parameters to consider when it comes to formulation development of drug entity various properties of the drug such as solubility. However, this hyper branched three dimensional carrier has successfully demonstrated its solubulisation and drug carrying capacity for a variety of hydrophobic drug molecules.

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