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Review

Dendrimers: A versatile nanocarrier for drug delivery and targeting

Atul P. Sherje*, Mrunal Jadhav, Bhushan R. Dravyakar, Darshana Kadam

Department of Pharmaceutical Chemistry & Quality Assurance, SVKM's Dr. Bhanuben Nanavati College of Pharmacy, Vile Parle (W), Mumbai 400 056, India

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ABSTRACT

Dendrimers are novel polymeric nanoarchitectures characterized by hyper-branched 3D-structure having multiple functional groups on the surface that increases their functionality and make them versatile and biocompatible. Their unique properties like nanoscale uniform size, high degree of branching, polyvalency, water solubility, available internal cavities and convenient synthesis approaches make them promising agent for biological and drug delivery applications. Dendrimers have received an enormous attention from researchers among various nanomaterials. Dendrimers can be used as a carrier for diverse therapeutic agents. They can be used for reducing drug toxicities and enhancement of their efficacies. The present review provide a comprehensive outline of synthesis of dendrimers, interaction of dendrimer with guest molecules, properties, characterization and their potential applications in pharmaceutical and biomedical field.

1. Introduction

The use of many therapeutic agents is restricted due to their poor solubility, toxicity and stability problems obstructing their clinical application in spite of showing excellent potency (Madaan et al., 2014). Hence, development of delivery system capable of delivering drug efficiently is needed. Many polymers have been demonstrated as drug delivery vehicles traditionally (Brannon et al., 2004); but poorly defined chemical structures (related to the average molecular weight of the polymers and their polydispersity) is a major problem associated with them. Researchers are making attempts to improve on these problems. Researchers have explored nanotechnology to overcome these problems and to improve physicochemical and biological properties of these agents resulting in increased solubilisation, bioavailability, and drug targeting (Gradishar et al., 2005; Ko et al., 2013; Awada, 2014). Many nanoparticle based therapeutic products are available commercially and some are under clinical and pre-clinical trials (Northfelt et al., 1998; Harries et al., 2005). The use of nanotechnology for drug delivery and targeting has proven substantial prospective in improving drug safety and reducing drug-related toxicity. Furthermore, the great concern of scientists in development of a single system capable of delivering therapeutic, targeting and diagnostic agents has directed the design of novel class of nanoparticles as multifunctional platforms (Madaan et al., 2014). Among various nanomaterials, dendritic nanostructures have appealed focus of researchers due to their distinctive physiochemical and structural properties (Lee et al., 2005; Svenson and Tomalia, 2005; Hao-Jui and Jason, 2017).

Dendrimers are well-defined homogenous three-dimensional structure of nanosize comprising of tree-like branches (Srinivasa and Yarena, 2007; Elham et al., 2014). Dendrimers have grabbed a great attention in the field of drug delivery to attain controlled drug delivery and in development personalized medicine systems (Dendrimers, 2017). Vogtle et al in 1978 was the pioneer in making first attempt to design and synthesize dendritic structures (Vogtle et al., 1978). These molecules were originally known as "cascade molecules". After several years of this report, Tomalia's group established a new category of cascade molecules containing amides having relatively smaller structures (Tomalia et al., 1985). Tomalia et al. named these new class of dendritic macromolecules as "dendrimers". The dendrimer name is derived from Greek words "dendros" which means "tree or branch" and "meros" meaning "part" (Madaan et al., 2014; De Brander et al., 1993). At the same time, Newkome's group reported synthesis of analogous macromolecules and named these structures as "arborols", a Latin word "arbor" meaning a "tree".

Dendrimers show characteristics features of both molecular chemistry (due to their step by step controlled synthesis) and polymer chemistry (as it is made up of monomers) (Caminade et al., 2005; Malik et al., 2012). The properties of dendrimers were found to be very different from conventional polymers. In addition, due to their nano-size structure dendrimers extends important applications in the evolving nanomedicine research. They can be used as an efficient delivery system, or carrier system for therapeutic agents (Madaan et al., 2014). VivaGel®, is a first dendrimer-based commercial medical product and many systems are now in clinical trials (Buhleier et al., 1978; Kannan

* Corresponding author at: SVKM's Dr. Bhanuben Nanavati College of Pharmacy, V. M. Road, Vile Parle (W), Mumbai 400 056, India.
E-mail address: sherjeap@gmail.com (A.P. Sherje).

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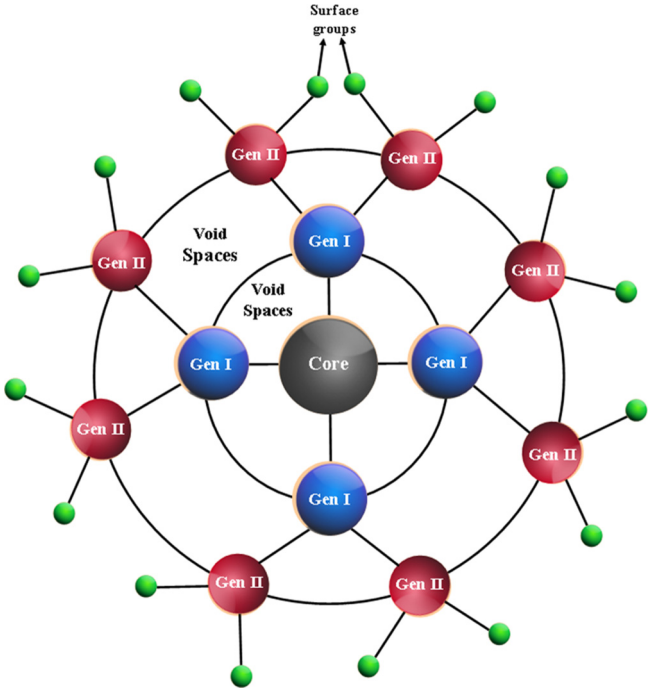

Fig. 1. Schematic representation of dendrimer (Gen = Generation).

et al., 2014). The chemistry of dendrimers is one of the most attractive and rapidly emerging areas of chemistry. The distinctive structure of dendrimers offers diverse prospects for multivalent host-guest interactions (Elham et al., 2014; Boris and Rubinstein, 1996; Spataro et al., 2010).

2. Structure and types of dendrimers

2.1. Structure

Due to well-ordered synthesis and hyper-branched architecture, dendrimers exhibit distinctive features (Caminade et al., 2012). Dendrimers are synthetic nano-architectures nearly 2–10 nm in diameter. They are three-dimensional, hyper-branched and monodisperse structure containing central core surrounded by peripheral groups. The dendrimer typically consists of (a) a central core (single atom or group of atoms), (b) building blocks containing many layers of repeating units known as generations, and (c) numerous functional groups on the surface which play a key role in their properties (Tomalia, 2005; Noriega-Luna et al., 2014) (Fig. 1).

The central core of dendrimers is comprised of an atom or a group of atoms to which branches of carbon and other elements are added through sequence of chemical reaction which is repeated to produce a spherical dendritic structure. However, some of the dendrimers like PAMAM does not have proper spherical structure (Elham et al., 2014; Zimmerman, 1997; Zeng and Zimmrman, 1997). The central core is encircled by extensive branching leading to numerous interior layers containing repeating units. Within the voids of dendrimer building blocks, flexible spaces are formed which facilitates encapsulation of guest molecules. The number of branching points (focal points) from central core to the surface is termed as “generation number” (Tomalia, 2005; Noriega-Luna et al., 2014). For example, a dendrimer holding five branching points is referred as “fifth generation”, denoted as “G5-dendrimer”. Hence, a fifth generation polyamidoamine (PAMAM) dendrimer is denoted as G5-PAMAM. The core part of the dendrimer is sometimes denoted as “zero” generation (G0) and hence does not present focal points in dendrimer structure. The dendrimer “shell” is the region between the focal points (Boas et al., 2006).

The outermost third part of a dendrimer is the surface containing many functional groups which can be tailor-made to interact with the external groups or molecules. The physicochemical properties of dendrimers depends on the branching units and the surface functional group (Semwal et al., 2010; Kalomiraki et al., 2016). The functional groups present at the surface are also called as “terminal group” or “surface group”. For example, a typical dendrimer holding amine functional groups at the surface are called as amino-terminated dendrimers.

During synthesis of dendrimers, increase in each generation (G) approximately doubles the molecular mass of dendritic structure (Hao-Jui and Jason, 2017). The numerous functional groups present at the surface of dendrimers has a vital role in determining their physicochemical properties and biological interactions (Caminade and Turrin, 2014). Hence, chemical alteration of the surface groups can be used for modulating cellular interactions and distributions of dendrimers in biological system (Malik et al., 2000; Hong et al., 2006; Yang et al., 2014; Yang et al., 2012; Hong et al., 2004).

A dendritic structure without a core is named as “dendrons”. A diverse type of dendrimers can be synthesized by connecting two or more dendrons together (Ex. convergent synthesis). A commercially available “Frechet” type of dendrons is demonstrated in the covalent and non-covalent association of dendrimers (Boas et al., 2006; Hawker and Frechet, 1990; Hawker and Frechet, 1990; Hawker et al., 1993).

2.2. Types of dendrimers

2.2.1. Polypropylene imine (PPI) dendrimers

Polypropylene imine (PPI) is the oldest known dendrimer introduced by Vogtle (Buhleier et al., 1978; Vogtle et al., 1978) describing the propylamine spacer moieties. They generally consist of poly-alkylamines with primary amines terminal groups and interior is comprised of several of tertiary tris-propyleneamines. PPI dendrimers have been studied in material and biological sciences. Sometimes “polypropylene amine” (POPAM) and “diamino butane” (DAB) dendrimer names are also used as an alternative term to PPI dendrimers. Polyethylene imine (PEI) dendrimers is a subclass of PPI dendrimers consisting of diaminoethane or diamino propane as functional groups of central core.

2.2.2. Polyamidoamine (PAMAM) dendrimers

PAMAM is a type of dendrimer containing polyamide branches and tertiary amines as branching points. Tomalia and co-workers introduced PAMAM dendrimers in mid-1980s (Tomalia et al., 1985; Tomalia et al., 1984) after which they were studied widely by researchers. “Starburst” dendrimers, a trademark of PAMAM sub-class contains tris-aminoethylene-imine group as a core. The name has been given due to star-like appearance of these high-generation dendrimer structure when observed two dimensionally (2D).

2.2.3. Frechet-type dendrimers

These are the type of dendrimer recently established by Hawker and Frechet (Hawker and Frechet, 1990; Hawker et al., 1993) containing hyper-branched architecture of poly-benzyl ether. Frechet dendrimers contains –COOH groups as the terminal groups and thus offering good branching point for modulation of terminal group functionalization. In addition, the presence of these polar terminal groups helps to enhance solubility of this class of dendrimers in aqueous media and polar solvents (Elham et al., 2014).

2.2.4. Core-shell tecto dendrimer

These are dendritic structures in which dendrimer molecule is used as a core surrounded covalently by shell of other dendrimers. Usually, the generation number of the core is more than the surrounding dendrimers. The attachment of additional shells is controlled by synthetic procedures allowing construction of nanoscale region of 1–100 nm (Li