Review Article

Dendrimers as drug delivery systems; the benefits and challenges

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ABSTRACT

Dendrimers as nanostructured macromolecules have ideal capabilities in entrapping and/or conjugating the high molecular weight hydrophilic/hydrophobic cargos by host-guest connections as well as covalent bonding, respectively. Besides, dendrimers are recognized for their distinct buildings, flexibility in drug delivery, and high functionality whose possessions resemble with biomolecules. Dendrimers can be used to deliver nucleic acid-based drugs such as siRNA, shRNA and miRNA alongside chemotherapeutic agents into cells with no damaging or deactivating effects on the DNA. For selective targeting of drugs into cancer cells, dendrimers can be functionalized with targeting ligands such as antibodies and folic acid. The aim of the current review paper is to present an outline of dendrimers as drug delivery systems as well as the benefits and challenges.

1. Introduction

The medicine-based on nanotechnology, nanomedicine, offers a new route and a strong procedure of drug therapy that can progress drug performance and overcome restrictions [1-4]. Nowadays, nanotechnology offers methodologies to produce different compounds with an extensive range of applications, from simple nanoparticles (NPs) to more complex buildings of biological and inorganic macromolecules [5-8]. Multi-functional structures in nanometric range may convert to the basis of medicine in the near future. Nanotechnology plays serious role in cancer treatment due to the application of different nano-vectors such as dendrimers, micelles, liposomes, carbon nanotubes (CNTs), metal NPs, synthetic and natural polymer NPs, and polymer–drug conjugates [9-11].

Dendrimers are unique nanoarchitecture structures with excellent characteristics such as nanometric size, a globular 3D shape, and monodispersed unimicellar nature. The other properties like drug encapsulation, solubilizing together with passive targeting also contribute to the therapeutic usage of dendrimers [12]. According to recent reports, dendrimer-based combination chemotherapy (DCC) is a novel approach in targeted drug delivery into cancer cells [13]. DCC strategies involve co-delivery of two chemotherapeutic medications, the chemotherapeutic drug with anti-tumor metals and molecular agents, as well as co-delivery with dendrimer-coated magnetic NPs and combination of photodynamic therapy and chemotherapy. The aim of the current review paper is to present an outline of dendrimers as drug delivery systems as well as the benefits and challenges. The search process was performed using

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internet databases mainly PubMed and included in vitro and in vivo studies by means of MeSH keywords to recognize relevant published literature in English.

2. Properties of dendrimers

Dendrimers are one of the best recognized NPs due to unique properties like symmetrical structure, spherical shape, monodispersed, and branched structure. There are three main parts in the structure of a dendrimer; a central core, branches, and functional end groups on the surface. All three parts has reported to show critical functions, affecting the size, shape as well as the other features of the dendrimers [14]. The generation of a dendrimersdenotes to the number of repeated branching cycles that are formed throughout its preparation. For instance, if the branching is done onto the core molecule 3 times, the prepared dendrimer is a third-generation kind (G3) [15]. Figure 1 shows a G4 dendrimers structure with different types of targeting ligands in different sections of dendrimer.

Many advantages of dendrimers have been recognized comparing to other polymeric architectural systems. The characteristics of branched macromolecules in dendrimers are completely different from current linear polymeric materials [16]. Such differences are typically owing to the synthesis approaches. The traditional polymerization method generally produces polydisperse structures with different molecular weights, while dendrimers producing methods are able to generate homogeneous structures with uniform molecular weight [17]. Because of the spherical form as well as interior cavities, dendrimers are known as “host-guest” molecules, that they can display great encapsulation capabilities with the ability to deliver several compounds in their interior. Host–guest structures are composed of 2 or more molecules/ions that are kept together in inimitable structural connections. The forces other than full covalent bonds are involved among them.

Chemical and biological possessions of the dendrimers depend on surface terminal groups. The high number of surface functional groups has reported to be responsible for high solubility as well as permeability of dendrimers [18]. Sometimes, the terminal groups are extremely reactive and then may need to further alterations. Post-modification of the surface of the macromolecule is performed either to vary the physicochemical possessions or to make a specific activity like catalytic or therapeutic [19].

3. Type of dendrimers

Dendrimers can be classified based on their shape, internal cavities, generation, and end functional groups. Some types of main dendrimers are classified in Table 1.
Table 1. Type of dendrimers.

<table>
<thead>
<tr>
<th>Type of dendrimer</th>
<th>Main points</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAMAM (Poly Amido Amine) Dendrimer</td>
<td>• Synthesized through the divergent procedure.</td>
<td>[20]</td>
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<td></td>
<td>• Ammonia or ethylenediamine are used as initiator core.</td>
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<td></td>
<td>• Condensation of DNA followed by transfection owing to possess positive surface.</td>
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<td></td>
<td>• A diamine like ethylenediamine as the core of PAMAM reacted with methyl acrylate, and then another ethylenediamine to form the generation-0 (G-0) PAMAM.</td>
<td>[21]</td>
</tr>
<tr>
<td>PPI (Poly Propylene Imine) Dendrimer</td>
<td>• Amine terminated hyper-branched macromolecules.</td>
<td>[22, 23]</td>
</tr>
<tr>
<td></td>
<td>• Synthesized by divergent approach.</td>
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<td></td>
<td>• 1, 4-diaminobutane is used as dendrimer core.</td>
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<tr>
<td></td>
<td>• Some other molecules with primary or secondary amine groups may also be utilized as core in their synthesis.</td>
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<tr>
<td>Liquid crystalline (LC) dendrimers</td>
<td>• Consist of mesogenic LC monomers.</td>
<td>[16, 24]</td>
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<td></td>
<td>• Usually designed by rod-like (calamitic) or disk-like (discotic) molecules.</td>
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<td></td>
<td>• The lack of mesomorphism is observed for the fifth-generation dendrimer due to its inability to reorganize into a cylindrical shape.</td>
<td></td>
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<tr>
<td>Core Shell (tecto) dendrimers</td>
<td>• Possess a well-ordered structure due to controlled covalent bond of building blocks.</td>
<td>[16, 25-27]</td>
</tr>
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<td></td>
<td>• Composed of a core dendrimer that may or may not contain a cargo.</td>
<td></td>
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<tr>
<td></td>
<td>• Have simple synthesis procedure.</td>
<td></td>
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<tr>
<td>Chiral Dendrimer</td>
<td>• Have different construction of constitutionally but are chemically similar with a chiral core.</td>
<td>[16, 28]</td>
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<td></td>
<td>• Chiral, non-racemic dendrimer that have ideal stereochemistry are proper for applications in asymmetric catalysis and chiral molecular recognition.</td>
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<tr>
<td>Hybrid dendrimers</td>
<td>• Combination of dendritic and linear polymers in hybrid block or graft copolymer systems.</td>
<td>[31]</td>
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<td></td>
<td>• are applied as surface active agents, compatibilizers or adhesives, or hybrid dendritic linear polymers owing to the small dendrimer segment coupled to multiple reactive chain ends provides an opportunity to use them.</td>
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<td></td>
<td>• Can produced from various polymers with dendrimers generated the compact, rigid, uniformly shaped globular dendritic hybrids.</td>
<td></td>
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</table>

4. Drug delivery systems based on dendrimers

An extremely branched building can be used as an appropriate targeted drug delivery carrier through attaching different ligands [32]. Outstanding possessions of dendrimers are responsible for their great advantages comparing to other delivery systems. The three-dimensional construction alongside with multifunctional terminal groups as well as numerous internal cavities let dendrimers to transport different cargoes. These cargoes can captured within the scaffold or attached to the surface of dendrimers. These structures are known by high loading efficiency as well as stability in path of intracellular transportation. According to literature, dendrimers can progress drug’s solubility, spread the cargo’s blood circulation time through decreasing their removal, preserve drug concentrations higher than the minimal therapeutic dose in the plasma, and protect them from probable environmental damages. Dendrimers as systems proper for drug delivery can apply to avoid the resistance mechanisms and simplify the carriage of the drug directly to target cells without involving normal cells [33].

From some point of views, dendrimers are different compared to conventional polymers; they are in nano-meteric size and spherical shape that own a high grade in uniformity of molecular structure, and tolerate of high surface modifications [34]. A large drug capturing can also confer by the unique structural configuration of dendrimers. Such a cargo loading may perform through numerous methods such as the surface adsorption (that benefit from ionic interactions), entrapment within microparticles, or direct covalent bonding to the surface functional groups. These outstanding possessions convert dendrimers to an ideal system for simultaneous delivery of hydrophobic and hydrophilic drugs [33]. The potential applications of dendrimers in medicine have made considerable attention in this regards. As an example, there are numerous alterations of dendrimers's exterior groups which permit to attain antibody or peptide conjugates with, or to form dendritic boxes that capture guest molecules [30,32]. Poly (amidoamine), or PAMAM, is possibly the most famous dendrimer.

5. Challenges of using dendrimers in drug delivery

Some properties of surface groups such as charge affects the cytotoxic action of dendrimers. Irrespective of surface composition and molecular structure, cationic dendrimers are more cytotoxic and hemolytic than anionic and neutral dendrimers, owing to their non-specific affinity to cell membranes with negative charge. Their toxic effect is generation-dependent and increases with the number of surface groups [33] while neutral and negatively charged dendrimers do not show cytotoxic effect in vitro. To enable diagnostic and therapeutic uses, it is required to decrease the toxicity of positively charged
dendrimers. To this end, some chemical alterations of terminal groups have been presented which improve the targeting potential, meaningfully extend blood half-life, improve bio-distribution and biocompatibility pattern of dendrimers [34].

Conclusion

Outstanding properties of dendrimers like their size, shape, branching ability, and their surface modifiability convert these compounds to an ideal vehicle in different medical fields such as drug/gene delivery. These possessions present the dendrimers as smart selections for drug delivery. The unique properties of dendrimers have confirmed vast flexibilities in diversity of applications. However, further researches are required to identify their absorption or uptake mechanisms through biological membranes as well as in vivo stability.

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References


