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Review article

Dendrimers and their supramolecular nanostructures for biomedical applications

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ABSTRACT

Pharmaceutical nanotechnology is the field of materials science that focuses on techniques to process raw materials to produce nanostructures with desired properties for pharmaceutical applications. Nanostructures can be roughly divided into surface textures, tubular structures or particles, depending on how many of their dimensions are on the nanoscale. The structures may also be divided into hard and soft structures, depending on their physical properties. There has been lately a growing interest to study soft supramolecular structures. In this review, the main focus is to briefly introduce the reader to various aspects of dendrimers, including Janus dendrimers, and supramolecular structures and then focus on recent studies dealing with application of dendrimer-based supramolecular structures in the pharmaceutical field.

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1. Introduction

Polymers can be broadly divided into four classes based on their primary structure: 1) linear, 2) cross-linked with side-chains or side-functional groups, 3) branched, and 4) perfect dendrimers [1]. The primary structure of perfect dendrimers branches periodically and in a precise pattern. The name of an individual dendrimer is derived from the branching pattern and the generation of the dendrimer, i.e. an ordinal number stating the number of times the pattern is repeated. Generally, dendrimers display an open structure at low generations and become more globular and dense as the

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generations increase. Dendrimers without globular core-shell topology are sometimes termed dendrons to emphasize this detail. Dendrimers have intrinsic and unique features, e.g. high structural fidelity due to controlled iterative synthesis methods, and a high number of functionalities present in the intermediate and surface layers [2–4]. Especially dendrimers with globular core-shell topology can be viewed as nanoscale atom mimics [5] that are capable to aggregate and form nanoscale mimics of molecules via surface interactions [6].

Structural effects of intermolecular interactions are studied in supramolecular chemistry. Among aspects covered are self-assembly, i.e. the hierarchical process where molecules spontaneously arrange into supramolecular assemblies that further self-organize into supramolecular structures and systems [7], and self-curing, i.e. ability of the supramolecular structures to reform after being damaged [8]. Supramolecular self-assembly processes may be driven by phase separation, a complex phenomenon where components of chemical mixtures or chemically distinct domains of molecules get spatially separated. One of the most ubiquitous self-assembly processes is the hierarchical organization of amphiphilic molecules into structures such as micelles, rods and vesicles [9]. Molecular recognition driven self-assembly processes differ from the phase separation driven ones since in this case a connection is formed when chemically different domains pair through interactions precisely complementing each other. A number of examples demonstrating supramolecular polymers formed via molecular recognition driven self-assembly processes and further phase separation driven self-organization of such polymers into complex structures, e.g. vesicles, may be found in a recent review [10]. As a specific example of a molecular recognition driven process, the host-quest chemistry between adamantane-modified hyperbranched polyglycerol and cationic β-cyclodextrin derivatives has been utilized to design self-assembling dendritic polymers for non-viral gene delivery [11].

Supramolecular structures can be manifold, one example being supramolecular coatings. The coating molecules form monolayers upon adsorption to a solid support. An interesting coating study was made with amphiphilic peptide coatings incorporating a terminal L-lysine dendron and a terminal fatty acid on an oligopeptide [12]. Further, the dendrons were equipped with one or two cell adherence motifs. The coatings were then attached to the polymeric scaffold whereupon they adapted supramolecular β-sheet structures. In comparison to bare scaffolds and scaffolds coated with a linear peptide coating, the scaffolds coated with the L-lysine dendron bearing coatings showed improved colonization of the scaffold surface by human bladder smooth muscle cells (SMCs) and enhanced penetration of the cells into the scaffold. Thus, the dendron bearing coatings have potential to be used in bladder tissue regeneration applications. The results were speculated to be due to either improved accessibility of the adhesion sequences to the SMCs, or due to non-specific electrostatic attraction between the positively charged amines of the L-lysine residues and the SMCs.

Dendrimers and dendrons have been shown to self-assemble into hierarchically organized structures [13,14], mediate chirality into structures [15,16], glue supramolecular structures [17], and facilitate the formation of crystalline complexes with viruses [18]. There are already reviews about dendrimers [19] and dendrimer-based supramolecular structures [20] in pharmaceutical and

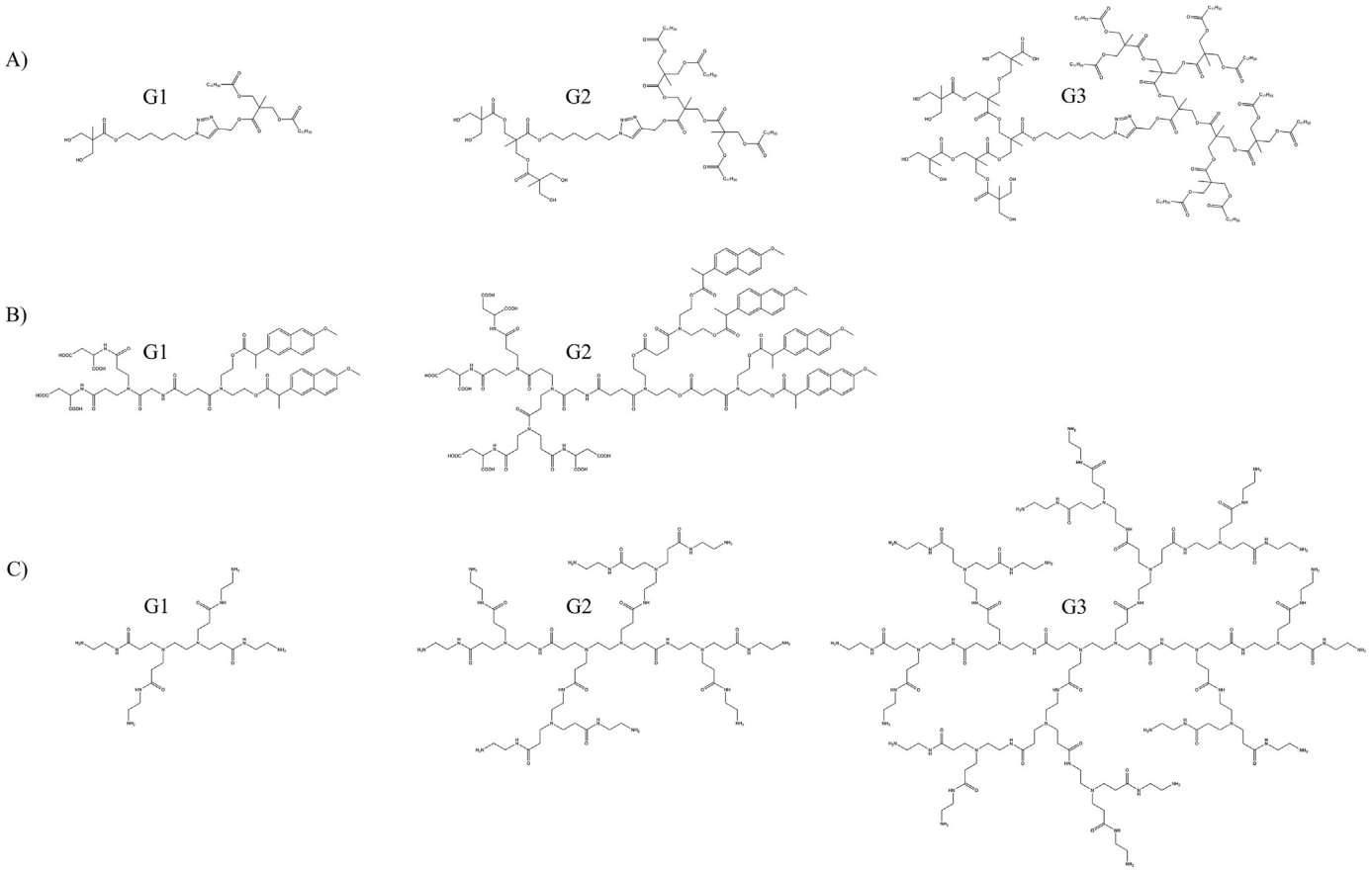

Fig. 1. Examples of the chemical structures of dendrimers. A) Generations 1–3 of Janus dendrimers with a triazole in the core [60], B) generations 1–2 of Janus dendrimers with aspartic acid as targeting moiety [69], and C) generations 1–3 of PAMAM dendrimers.