Lecture 9. Linear nanopolymers. Dendrimer nanoparticles

The purpose of the lecture: to familiarize students with linear nanopolymers and dendrimer nanoparticles.

Expected results: students getting information about linear nanopolymers and dendrimer nanoparticles.

Structure

Polymeric nanoparticles are one of the most investigated nanoparticles as drug delivery vehicles. Biodegradable nanopolymers can be functionalized to improve their biocompatibility and drug targeting to particular organs/tissues. They can also be used as carriers of DNA in gene therapy, and in their ability to deliver proteins, peptides, and genes through oral administration.

Synthesis

Two basic procedures are used for synthesis of polymer nanoparticles: (1) the dispersion method, in which preformed polymers are used for synthesis; and (2) the polymerization method, in which synthesis occurs via direct polymerization of monomers.

1. Dispersion methods: In the solvent evaporation method, oil-in-water emulsions are subjected to either high-speed homogenization or ultrasonication, followed by evaporation of the solvent. In the nanoprecipitation method, polymers are suspended in aquatic and organic solvents to precipitate polymer nanoparticles. Salting-out involves dissolution of polymer and drug in an organic solvent (such as acetone) and then emulsification into an aqueous gel containing the salted-out electrolytes (magnesium chloride, calcium chloride, and magnesium acetate) or nonelectrolytes (sucrose) and a stabilizer (polyvinylpyrrolidone or hydroxylethylcellulose). For dialysis, the polymer is dissolved in an organic solvent and then dialyzed using an appropriate cutoff membrane against a miscible nonsolvent. The displacement of the solvent inside the membrane results in the progressive formation of homogeneous suspensions of nanoparticles. In the supercritical fluid technology, the polymer is dissolved in a supercritical fluid, followed by a rapid expansion of the solution into an appropriate solution for nanosized particles.

2. Monomer polymerization methods: In the emulsion method, a monomer is dissolved in a continuous aqueous solution. The polymerization is initiated when a monomer molecule collides with an initiator molecule that might be an ion or a free radical. Collisions among the monomer ions initiate chain growth. In the interfacial method, polymerization is carried out at the interface of two immiscible solvents, such as the monomers dissolved in an organic solvent and an oxidizing agent dissolved in an aqueous solution. In the microemulsion polymerization method, an aqueous solution containing the oxidizing agent and an organic solution containing the monomer are emulsified in the presence of a surfactant to prevent aggregation. In a controlled/living radical procedure, the radical-collision method is controlled. C/LR provides control over the molar mass, the molar mass distribution, the end functionalities, and the macromolecular architecture.

Functionalization of Nanopolymers

The overall strategies described earlier (metal nanoparticle section) are applicable for the functionalization of nanopolymers, except that nanopolymers exhibit no affinity for the thiol group. Therefore, covalent and noncovalent methods are used to functionalize nanopolymers with PEG.

Application of Polymer Nanoparticles

1. Cationic, but not anionic or nonionic, polymeric nanoparticles are internalized into the cells, suggesting the possibility of their application on gene therapy. The total number of particles is inversely proportional to their size.

2. Polymeric nanoparticles (1) increase the stability of volatile pharmaceutical agents; (2) offer protection of the drugs from the degradation enzyme of blood and liver, thus significantly improving their stability when given orally or administered by intravenous injection; and (3)

deliver a higher concentration of pharmaceutical agent to a desired location. They also facilitate selective cancer therapy by delivering vaccines, antibiotics, and anticancer drugs at the target site.

3. Polymeric nanoparticles are the starting material for synthesis of other advanced nanoparticles, such as dendrimers, nanospheres, and nanocapsules.

DENDRIMER NANOPARTICLES

Structure

Dendrimers are a class of three-dimensional molecules having a high degree of structural symmetry, a density gradient, and defined number of terminal groups that may be chemically different from the inner groups. The dendrimer nanoparticles are functional nanomaterials with unique electronic, optical, optoelectronic, magnetic, chemical, and biological properties.

Dendrimers are repetitively branched molecules that radiate from a central unit called the core. The number of branching points when going from the core towards the surface is called the generation number. Dendrimers having one branching point when going from the center to the periphery are called first generation (G1) dendrimers. An increase in branching points increases the generation numbers. For example, G4 dendrimers have four branches radiating from the core. Dendrimers have three components: a central core fourth generation, core (C)), an interior dendritic structure, the branches (G1eG4), and an exterior surface with functional surface groups.

The branches can be homologous (G2 top, G3 and G4 top) or heterologous (G2 bottom and G4 bottom.). The synthetic methodology, therefore, allows production of multifunctional dendrimers.

Types of Commonly Used Dendrimers

POLY (AMIDOAMINE) DENDRIMERS (PAMAM)

These dendrimers are synthesized from ammonia or ethylenediamine as the core reagent. Products up to generation have been synthetized. A modification of PAMAM is radially layered poly(amidoamineorganosilicon) (PAMAMOS) dendrimers that consist of hydrophilic, PAMAM, interiors, and hydrophobic organosilicon exteriors.

TECTO DENDRIMERS

These dendrimers are composed of a core dendrimer, surrounded by dendrimers designed to perform a specific function such as diseased cell recognition, diagnosis of the disease state, drug delivery, reporting location, or reporting outcomes of therapy. Multilingual dendrimers contain multiple copies of a particular functional group.

CHIRAL AND AMPHIPHILIC DENDRIMERS

Chiral dendrimers consist of constitutionally different but chemically similar branches to the chiral core. Amphiphilic dendrimers are built with two segregated sites of a chain enddone half is electron donating and the other half is electron withdrawing.

POLYMERIC DENDRIMERS

Fr_echet-type dendrimers are based on a poly-benzyl ether hyper-branched skeleton and carboxylic acid groups as surface groups. Therefore, rotation about the bonds between the rings is unable to change the structure of the molecule. These different types of dendrimers have unique properties that can be exploited for specific functions.

DNA-BASED DENDRIMERS

DNA is a helical polymer central to the genetic makeup of all organisms. Recently, polymeric DNA molecules have been designed that are important in nanomedicine including, but not limited to, disease screening and therapeutics. Synthetic DNA polymers generally belong to the following four topologiesdlinear, branched, dendritic, and networked. Linear DNA nanopolymers are simple structures used extensively in drug delivery. The branched DNAs usually contain Y-shaped subunits and sticky ends that connect two to four units to make dendrimers.

Branched DNA building blocks are also used to construct network DNA tiles and hydrogels.

Linear polymeric nanoDNAs form complexes with lipids, cationic polymers, and synthetic peptides that may get encapsulated within hydrogel nanoparticles.

Linear polymeric nanoDNA is synthesized using monodispersed, single-stranded DNA (ssDNA) that (1) recognize and bind to complementary sequences and form a double-strand DNA (dsDNA)da process known as hybridization. They may selfanneal to form unique tertiary structures such as dendrimers that can bind specifically to macromolecules. The DNA dendrimers overcome some of the limitations of the linear DNA: they are inherently multivalent and designed to contain different functional moieties on different branches that are connected anisotropically. DNA dendrimers have the advantages of traditional chemical dendrimers such as tunable size, diverse architecture, and availability of multiple surface groups; however, unlike the chemical dendrimers, the "sticky ends" of DNA dendrimers allow construction of nanostructures with specific functional moieties.

The dendrimeric DNA, however, lack rigidity in the structures, which prevents their selfassembly of ordered structures. This deficiency has been resolved by the development of networked DNA such as checkered-patterned DNA, hexagonal DNA, cross-shaped DNA, and starpatterned DNA lattices. The networked DNA include double crossovers, triple crossovers, and paranemic crossover structures with increased rigidity and planar format. A combination of these structures form DNA tiles that can be used to form more complex patterns. Lou et al. (2008) and Umet al. (2006) have developed a simple method using branched DNAs having unique sticky ends that were used to construct dendritic DNAs. The peripheral Y-DNAs (with sticky ends complementary to the core Y-DNA) were ligated to the initial core to form the G1 dendrimeric DNA. Subsequent generations (G2, G3, G4, etc.) were produced by repeatedly ligating peripheral Y-DNAs to the sticky ends of the previous generation.