Journal of Simulation and Analysis of Novel Technologies in Mechanical Engineering
15 (1) (2023) 0051~0061

Review paper

The mechanical performance of silk and collagen nanoparticles for dental applications

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(Manuscript Received --- 28 Oct. 2022; Revised --- 18 Jan. 2023; Accepted --- 19 Feb. 2023)

Abstract

Today, great interest has been generated by dental science and engineering researchers to use bio-based nanoparticles to deliver therapeutic molecules such as drugs, genes, and tissue engineering. Controlling particle size, charge, surface morphology and release rate of loaded molecules is important for using nanoparticles based on biopolymers and bioactive ceramics such as tricalcium phosphates (TCP) as drug/gene carriers. Recently, drug release systems and nanoparticle systems have attracted much attention as suitable carriers. Drug delivery systems are methods used to ensure that drugs reach the required areas in the body. Natural polymers such as proteins have attracted a lot of attention due to their biocompatibility properties with living organisms. Among polymers, silk fibers have attracted the attention of researchers in the field of textiles and medicine due to their good properties such as low specific gravity, strength and high thermal resistance. In addition, their use as carriers of drugs, therapeutic genes and biomaterials for tissue engineering with applications in the field of dental and orthopedic materials has been reviewed.

Keywords: Mechanical properties, Silk, Tricalcium phosphate, Drug/gene carriers

1- Introduction

Nanotechnology has received much attention since the 1980s and has been adapted in many engineering fields such as dental materials, orthopedic, mechanics, and biomedicine [1-2]. In particular, nanotechnology has led to significant advances in biomedical fields such as controlled drug/gene delivery, tissue engineering, site-specific imaging, and DNA structure [2-3]. Among nanomaterials, ceramics nanoparticles have contributed to progress in the field of dental materials [1-4]. In particular, therapies using nanoparticles have been widely obtained for the treatment of cancer, diabetes, allergies, infections, bone substitute for orthopedic and dental science

[5-6]. The polymer nanoparticles have been used in therapeutic applications is the fact that nanoparticles are the same size as proteins. Their large surface can also provide the possibility of displaying a large number of surface functional groups such as ligands. In addition, nanoparticles have a rapid absorption and release behavior due to their high diffusion and volume change abilities. Also, the particle size and surface characteristics of nanoparticles can be controlled [7-9]. The membrane currently used is mainly derived from animal tissue such as pig skin collagen, but new materials made using silk offer better stability and biological security and are less likely to cause dental infection.

Several surface modifications are covalent bonding between surface and functional molecules or polymers and layer-by-layer assembly [10-14]. In particular, these nanoparticles are often used as biomaterials for carriers of therapeutic molecules such as drugs, genes and scaffolds. Although polymeric nanoparticles are difficult to scale up, low drug loading capacity, and wide size distribution have attracted increasing attention from chemists, biologists, engineers, and pharmaceutical scientists because of the possibility of delivering bioactive compounds to cells, and organs [15-19].

Polymeric nanoparticles can be produced in a wide range of sizes and types which retain a topical medicinal agent for weeks.

Therefore, in this review, we focus on the use of various biopolymers as biomaterials for drug/gene delivery as well as tissue engineering applications. Synthetic polymers have adjustable kinetic and mechanical properties. Proteins have several advantages over synthetic polymers because they can be metabolized to harmless peptides by digestive enzymes, while synthetic polymers may accumulate in the body above a certain molecular weight and lead to toxic degradation products [20-36]. Due to the presence of functional groups on the surface of the nanoparticles, protein-based nanoparticles offer various possibilities for surface modification. The polysaccharides proteins are digested by specific enzymes. Polysaccharides are superior to synthetic polymers such as poly (ethylene glycol) as far as they prolong blood circulation time. In this research, types of polymer and ceramic nanoparticles based on collagen and gelatin were investigated. This article aims to consider the bone tissue engineering which can be used as a special case of DDS to perform controlled delivery of cells.

2- Nanoparticles for drug/gene delivery

In recent years, a number of drug/gene-loaded polymeric nanoparticles have been developed as drug carriers, and their circulation mechanism in the human body has been widely investigated. As nanoparticles containing drugs or genes are injected into the body, they pass through epithelial barriers and circulate in blood vessels before reaching to the target site. Then, the loss of nanoparticles from blood circulation occurs in tissues. In the continuous vascular endothelium in healthy tissues, nanoparticles eliminate from the bloodstream via the paracellular route, intracellular process, or membrane transport. In vascular endothelium filled in pathological tissues, the gaps of the fenestration sites on the endothelium are much larger (100 nm to 2 μm) than in healthy tissues (2 to 6 nm) [37-44]. Therefore, the nanoparticles pass through the holes and thereby increase the

penetration of the drug in the tissues and accumulate the drugs in the tumor sites, which is called "enhanced penetration and persistence effect". It should be noted that the fenestration of tumor vessels varies depending on numerous factors such as the type of cancer, the stage of the disease and the location in the body. In addition, fenestrations and vessels can undergo changes under various pathological conditions. For example, tumor growth causes the formation of new vessels characterized by discontinuous endothelium with large springs of 200-780 nm that allow the passage of nanoparticles. There should also be particle toxicology because they contain various interactions of nanoparticles with fluids. Cells and tissues that begin at the port of entry and then travel through a wide range of possible pathways to target organs. At the site of final persistence in target organs, nanoparticles may stimulate mediators that may activate inflammatory or immune responses [45-58]. These reasons and the design of nanoparticles based on biopolymers with specific sizes is one of the most important criteria for the application of delivery carriers as shown in Fig. 1.

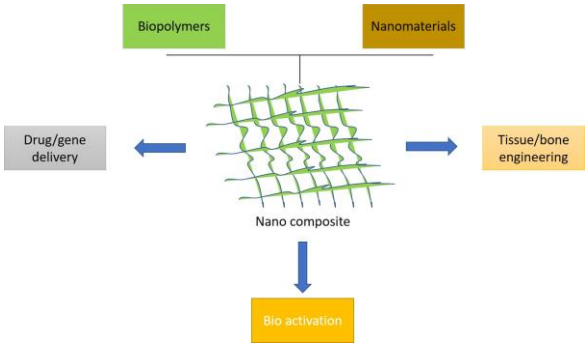

Fig. 1 Polymer matrix Nanocomposite for tissue engineering

The nanoparticle shape, surface charge, and surface specificity play an important role in intercellular transport because they all affect the mechanism of cellular internalization through endocytosis. In addition, to achieve site-specific delivery and release of bioactive drugs with the required amount, the type of polymers, particle size, solubility, biodegradability and surface properties should be considered. Fig. 2 shows the various characterization technique for synthesized nanoparticles for biomaterials domain. By responding to stimuli such as temperature, pH, or ionic strength, the carriers may disintegrate or diffuse to release the encapsulated drugs.

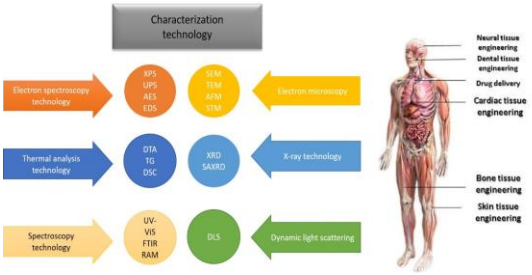

Fig. 2 Characterization technique for synthesized nanoparticles for biomaterials domain

Introducing stimuli sensitivity to carriers is critical for drug delivery system (DDS) applications to achieve controlled release of drugs from nanoparticles after aggregation at a specific site. In particular, adding pH sensitivity to nanoparticles is effective for DDS application. Because of the difference in the extracellular matrix (ECM) of normal tissue (pH 7.2-7.4) and many solid tumors (pH 6.2-6.9). Gene therapy has been used in many different diseases such as cancer and cardiovascular diseases (CVD) [59-63]. The concept of human diseases may be cured by transferring genetic material to specific cells of the patient to supply the defective genes responsible for the disease. To transfer genes to a specific location, genes must escape processes that affect the state

of macromolecules. In addition, gene degradation by serum nucleases should be avoided. Drug delivery carriers must be small enough to enter cells and pass into the nucleus. They must also have the ability to escape endosomal-lysosomal processing and follow endocytosis [62-69]. While both viral and non-viral vectors have been developed for gene delivery, non-viral vectors have been studied more due to their low immunogenicity and ease of control of their properties. Therefore, cationic polymers have the potential to complex DNA as non-viral vectors for gene therapy applications. To introduce this property to the surface of nanoparticles, the incorporation of cell-specific ligands to the surface of nanoparticles allows the expression of targeted transgenes. For example, nanoparticles of genes and cationic polymers can be modified with proteins (category, transferrin or antibodies/antigens) to enable specific cell targeting and enhance gene transfer. Nitric oxide-releasing substances have also emerged as potential treatments that utilize the broad biological roles of Nitric oxide. According to studies, Nitric oxide has antimicrobial effects and plays a role in wound healing process as shown in Fig. 3.

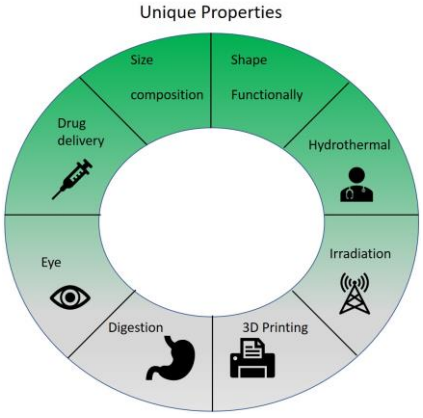

Fig. 3 Biopolymers have various applications in medical, food and pharmaceutical industries

3- Nanoparticles for dental application

Bone tissue engineering can be considered as a special case of DDS, which aims to perform controlled delivery of cells. Controlled release of therapeutic agents increases the efficiency of bone tissue engineering for treatment of maxillofacial fracture by dentist. The biological functions of encapsulated drugs and cells can be greatly enhanced by designing biomaterials with controlled organizations at the nanometer scale. Incorporation of gene transfer elements into the porous scaffold provides great potential to enhance the interaction between cells and the ECM environment because the delivery of genes to specific locations introduces signals and signs to cells in temporal manner for tissue growth. Therefore, therapeutic genes can enhance the integration of tissue microstructure, growth and absorption with beside tissues. In addition, gene delivery using biopolymers can act as DNA complexing agents and structural scaffolds for tissue engineering approaches. This combination of gene therapy and tissue engineering in a single system is thought to be a new treatment for regenerative medicine. The local gene delivery system using gene-activated matrix (GAM) combines these two strategies and acts as a local bioreactor with gene expression therapy and provides a structural template to fill the lesion defect for cell adhesion, proliferation and ECM.

4- Protein/polypeptide nanoparticles

4-1- Protein-based nanoparticles

Proteins are naturally derived polymers that are beneficial in terms of biodegradability, low toxicity, non-antigenicity, high nutritional value, high stability, and binding capacity of various drugs such as paclitaxel and ibuprofen.

Interestingly, they have the ability to emulsify, gel, form and bind to water. Because of these unique properties that differ from any synthetic polymer, protein-based nanocarriers are promising candidates for drug and gene delivery. Naturally derived proteins such as collagen, elastin and fibronectin were initially used as biomaterials. Recently, genetically engineered proteins and polypeptides have been produced to manipulate the properties of biomaterials such as degradation speed, biocompatibility, cell penetration ability by generating new protein sequences, self-assembling new peptides, integrating different bioactive domains or protein motifs. Elastin-like polypeptides (ELPs) are the most commonly genetically engineered proteins. The preparation of nanoparticles from proteins enables researchers to obtain precisely formed nanoparticles because the molecular sizes of proteins are determined by their secondary structures. A variety of proteins such as silk, albumin, collagen and elastin are good examples of proteins that have been used to prepare therapeutic nanoparticles. In addition to protein-based nanoparticles, nanoparticles are also prepared from polypeptides (MW < 10,000) that mimic naturally derived proteins, which contain proteins property form α-helical, β-sheet, or random structures determined based on the types of amino acids.

4-2- Silk based nanoparticles

Silk proteins are promising biomaterials due to slow biodegradability, biocompatibility, self-assembly property, excellent mechanical properties (tensile strength and elastic modulus) and controllable structure and morphology. Silk proteins are produced by spiders and insects such as silkworms and form fibrous material. Recombinant silks are also synthesized by explaining the genetics, structure and biophysics of silk. Silk-based nanoparticles are often produced by silk fibroins. Stable, spherical, negatively charged and low-toxic silk nanoparticles (150-170 nm) were prepared from the fibroin solutions of domestic silk. These nanoparticles accumulated in the cytosol of mouse squamous cell carcinoma cells and significantly showed sustained release of loaded growth factors (GFs) over three weeks. Silk fibroin and chitosan polymers were non-covalently combined to form nanoparticles (<100 nm) for local and sustained therapeutic delivery of curcumin to cancer cells. Incorporation of bioactive agents such as drugs or peptides into silk-based nanoparticles is also an efficient way to deliver these molecules to target sites. Silk protein crystalline nanoparticles (40-120 nm) are conjugated with insulin through covalent cross-linking. To control the release rate of bioactive molecules loaded in silk nanoparticles, a dual DDS based on silk nanoparticles and molecular networks of silk hydrogels has been developed. The model drugs incorporated in silk nanoparticles and hydrogels indicated fast and stable release. This observation indicating the successful release of two drugs from silk hydrogel containing silk nanoparticles. In addition, nanoparticles composed of DNA and recombinant silk, which contain cell-penetrating peptide, tumor-localizing peptide or cationic sequences have been designed for gene therapy.

4-3- Collagen based nanoparticles

Collagen is the main component of the ECM which has been widely used as a

biological material for years due to its promising biocompatibility, low antigenicity and biodegradability. Although collagen forms hydrogels without the use of chemical crosslinks, the preparation of nanoparticles requires additional chemical treatments due to poor mechanical strength. For example, collagen nanoparticles are often prepared by electrostatic interactions with sodium sulfate, which is used as a solubilizing agent. Recent studies on the preparation of collagen-based nanoparticles (340 nm) by lipid vesicle cages showed that it provides the possibility to control the dimensions of the particles and the gelling environment during collagen polymerization. Due to the ease of controlling their particle size, large surface area, high absorption capacity, ability to disperse in water, and collagen nanoparticles which showed continuous release of various drugs. Gelatin is obtained from collagen by acid and alkaline hydrolysis consisting of glycine, proline and 4-hydroxyproline residues with the typical structure. Gelatin solution is subjected to coil-to-helix transfer, and then the helices accumulate by forming a collagen-like triple helix, which enables the formation of nanoparticles. In addition, their high number of functional groups on the polymer backbone can be used for chemical modifications such as cross-linking and addition of ligands. Therefore, gelatin is a biopolymer for the production of nanoparticles as a delivery carrier as shown in Fig. 4. Nitta et al. [68] investigate the biopolymer-Based Nanoparticles for Drug/Gene Delivery and Tissue Engineering. This study considers the effects of the nature of the materials and the fabrication process on the characteristics of the nanoparticles are described.

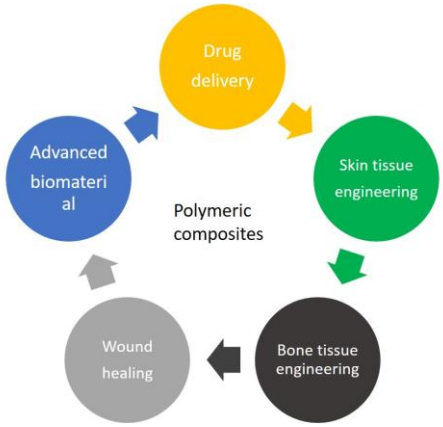

Fig. 4 Drug delivery, skin tissue, bone tissue, and wound dress application used natural polymeric composites for medical, food and pharmaceutical industries

4-4- Beta-casein based nanoparticles

Beta-casein (CSN2) is the main component of milk protein due to its amphiphilic nature easily assembles into a micellar structure with hydrophobic intermolecular interactions. The CSN2 have a suitable feature for application as delivery carriers. The spherical casein micelle has a hydrophobic interior surrounded by a hydrophilic k-casein layer that stabilizes the micelle through steric and electrostatic effects. Changes in temperature, pH, ionic strength, water activity, and high hydrostatic pressure treatment lead to changes in the size distribution of casein micelles due to the absence of a rigid three-dimensional (3D) structure. To use β-casein micelles for delivery carriers, stabilization of micelles by cross-linking is crucial. Cross-linking of lysine residues in casein by glutamine transglutaminase residues increased the intra-micellar stability of casein micelles. Chemical binders such as 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide have also been used to create thermally responsive nanoparticles from β-casein. To further stabilize casein nanoparticles, self-assembly of β-casein and lysozyme followed by thermal gelation of lysozyme

is used to entrap casein in the gel. The obtained nanoparticles have a spherical shape and their size depends on the pH of heat treatment (100 and 300 nm at pH 10.0 and 5.0, respectively) and the molar ratio of beta casein to lysozyme. Because beta-casein is an edible substance which used as a drug carrier for the oral delivery system. Several types of hydrophobic chemotherapy such as mitoxantrone, vinblastine, irinotecan, docetaxel and paclitaxel have been entrapped in beta-casein micelles to entrap drugs with the aim of drug release for oral delivery.

5-Conclusion

Controlling particle size, charge, surface morphology and release rate of loaded molecules is important for the use of biopolymer-based nanoparticles as drug/gene carriers. To obtain a nanocarrier for therapeutic purposes, a variety of materials and preparation processes have been investigated. This review focuses on the fabrication of biocompatible nanoparticles composed of biopolymers such as protein (silk, collagen, gelatin, beta-casein, and albumin), protein-mimicking polypeptides, and polysaccharides (chitosan, alginate, pullulan, starch, and heparin). The effects of the nature of the material and the manufacturing process on the properties of nanoparticles are described. In addition, their use as carriers of drugs, therapeutic genes and biomaterials for tissue engineering was investigated. Biopolymers are polymers that are produced from living organisms. Controlling particle size, charge, surface morphology and release rate of loaded molecules is important for using nanoparticles based on biopolymers and bioactive ceramics such as tricalcium phosphates as drug/gene carriers. To obtain a nanocarrier for therapeutic purposes, a variety of materials and preparation processes have been investigated.

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