A Review of the Biomaterial Applications of Zein

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Abstract: Plant protein has increasingly inspired the interest of researchers due to its safety, wide sources, and high performance and low cost. Zein, an important member of plant protein was used by the US FDA as a safe excipient for drug film packaging in 1985. In the past 20 years, reports on the application of zein in the fields of drug sustained-release material and tissue engineer scaffold materials have been constantly emerging, making the application of zein in the field of biomedicine a research focus. This review summarizes some of the application forms of zein in biomedicine, including drug loading, sustained-release material, and tissue scaffolding in the form of microspheres, fibers, and films. It is expected that this review will provide ideas for the use of zein in biomaterials industry.

1 INTRODUCTION

Zein is a degradable, hydrophobic plant protein originally isolated from whole white corn and named by John Gorham in 1821. According to protein solubility and sequence homology, it can be further subdivided into α-zein (19 and 22 kDa), β-zein (14 kDa), γ-zein (16 and 27 kDa), δ - Zein (10 kDa), of which α-zein has the highest content in corn, reaching 70-85% (Curtis, 1991). The zein originates is more hydrophobic attributed to its large number of hydrophobic amino acid residues, such as leucine, proline, alanine. The unique amino acid composition makes zein only soluble in acetone, acetic acid, aqueous ethanol and alkaline aqueous solution.

Early period, Zein was used to make regenerated fibers, but it was quickly replaced by synthetic fibers. Until 1985, the US FDA approved zein excipient for drug film coating as a GRAS mainly used in tablets (Anonymous, 1985). Thus, zein began to enter the period of medicinal use. In recent years, with some reports of the application of zein in drug delivery and tissue engineering, the application of zein has gradually become a hot spot in the field of materials. Zein can be made in various forms for using, and there are four commonly application: microspheres, nanoparticles, nanofibers and zein films.

2 APPLICATION OF ZEIN MICROSPHERES

Microspheres with an average diameter of 1 mm are designed for intravenous injection and oral administration of drugs. In 2005, Xinming Liu (Liu, 2005) prepared zein microspheres encapsulating ivermectin (IVM) drugs by using phase separation technology. The microspheres were characterized by scanning electron microscope and laser scattering particle size analyzer. In vitro studies showed that zein microspheres are suitable for the sustained release of IVM, and the system is suitable for use on some biologically active substances that require sustained release, See Figure 1.

3 APPLICATION OF ZEIN NANOPARTICLES

Particles with at least one dimension less than 1000 nm are defined as nanoparticles (Cristina, 2007), which have great potential for improving bioavailability and bioactivity due to their unique physicochemical properties (Emilie, 2010). The insoluble nature of zein in water makes it a good choice for the development of slow-release biopolymer nanoparticles.

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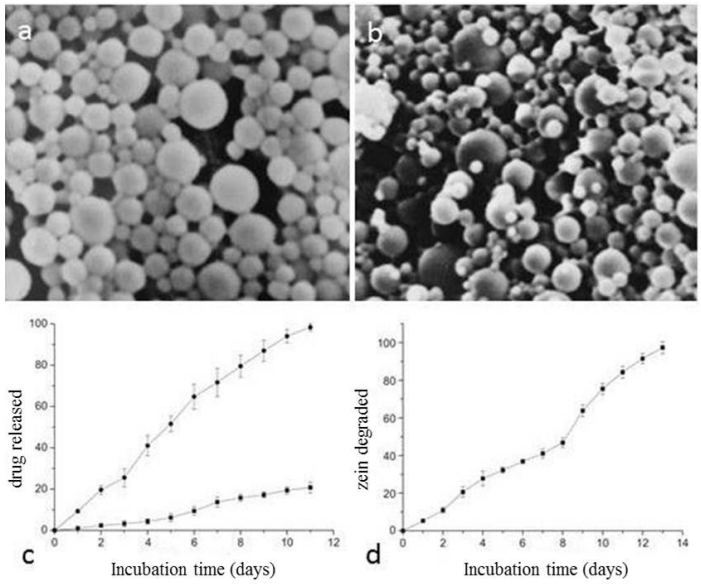

Figure 1: Scanning electron micrographs of IVM-loaded zein microspheres (a) Before lyophilization (b) after lyophilization (c) In vitro release profiles of IVM as a function of time from tabletted microspheres (d) from pepsin degraded tabletted microspheres (Liu, 2005).

Cranberry proanthocyanidins (CPs) have potential antioxidant functions and have certain applications in reducing cardiovascular disease and cancer. However, the oral bioavailability of CPs is very low, which limits its further application. In 2011, Tao Zou et al. (Zou, 2012) used an improved liquid-liquid dispersion method to prepare cranberry procyanidin-zein (CPs- Zein) nanoparticles, cell culture experiments show that CPs encapsulated in nanoparticles can reduce the toxicity to cells, See Figure 2.

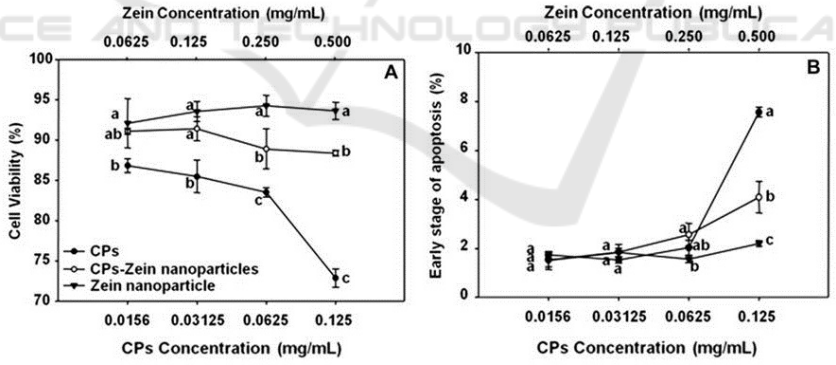

Figure 2: (A)Percentage of the cell viability, (B)the early stage of apoptosis (Zou, 2012).

Compounds with antioxidant effects have a certain role in the prevention and treatment of some cardiovascular diseases, tumors, etc., but most of these antioxidant compounds have the characteristics of low stability and low bioavailability, so the development of new drug delivery methods for the application of the compound is of great significance (Huang, 2017). Gallic acid (GA) is an active substance widely present in green tea, vegetables and fruits, and has antioxidant, anti-inflammatory, antibacterial and anti-tumor effects, but because gallic acid is unstable under high temperature, oxidation, light, etc., and the oral bioavailability is low, so its application is limited (Wang, 2018). Jose Agustin et al. (José, 2018) studied the preparation of gallic acid-loaded zein nanoparticles by electrospraying and demonstrated the potential ability of such nanoparticles to protect gallic acid. Figure 3. is the preparation process of gallic acid-loaded zein nanoparticles.

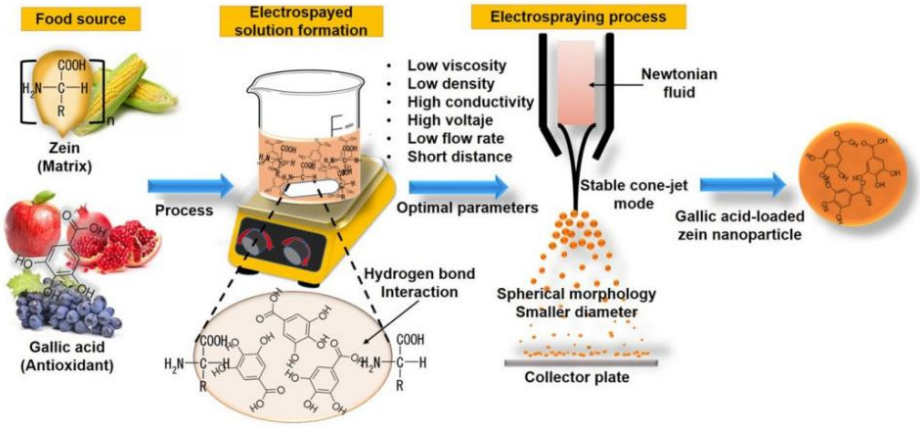

Figure 3: Preparation process of gallic acid-loaded zein nanoparticles (José, 2018).

4 APPLICATION OF ZEIN NANOFIBERS

The use of zein as fiber has a very long history. As early as more than 100 years ago, Ostenberg reported the first patent for the production of fiber with zein. Since then, various dry or wet spinning methods to prepare micro-sized corn gluten fibers have appeared one after another. In 2013, Weidong Huang et al. (Huang, 2013) used an improved coaxial electrospinning process to prepare ibuprofen (IBU)-loaded zein fibers, and in vitro dissolution experiments showed that the drug-loaded fibers could diffuse through typical Fickian diffusion. and the mechanism maintains sustained release in 10 hours. W. Nie et al. (Nie, 2012) prepared zein-polyvinylpyrrolidone (PVP) microfiber materials by electrospinning technology, He used ketoprofen as a model drug. Vitro dissolution experiments showed that the drug dissolution rate was related to the ratio of PVP, and fibers with different dissolution rates can be obtained by adjusting the ratio of zein and PVP. The drug sustained release model is shown in Figure 4.

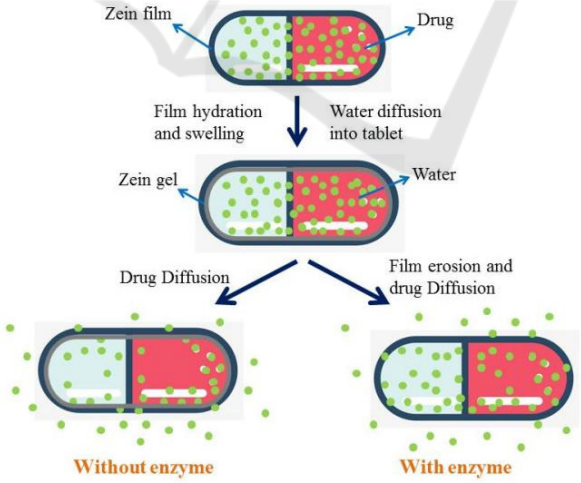

Figure 4: Proposed drug release process of zein-coated tablets (Nie, 2012).

Afeesh Rajan Unnithan (Unnithan, 2014) mixed cellulose acetate and zein, added streptomycin sulfate, to obtain a nanofiber skeleton with antibacterial effect utilizing electrospinning technology, applying polyurethane as a substrate. The material has good antibacterial properties, cytocompatibility, and promotion of coagulation, this indicates the potential application of this material in wound treatment.

In addition to applications in drug delivery, zein nanofibers have also begun to emerge as scaffolds for tissue engineering. In 2015, Peng Liu (Liu, 2015) used oxidized sucrose as a cross-linking agent to prepare a zein nanofiber scaffold using 3D electrospinning technology. The development laid the foundation, See Figure 5.

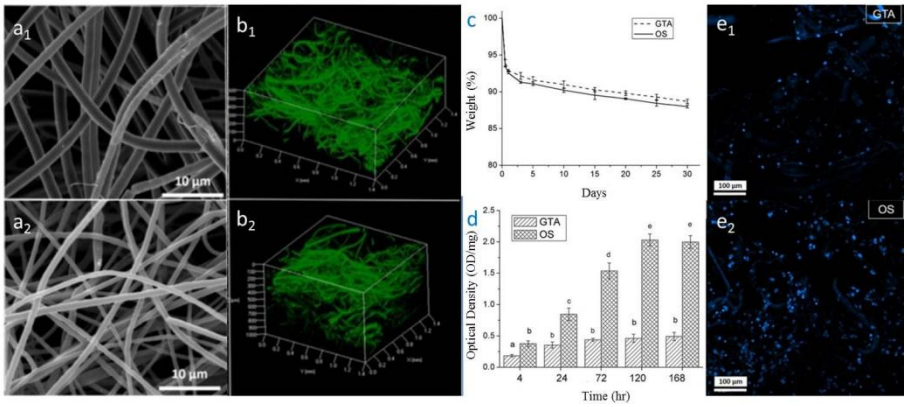

Figure 5. SEM images of the views (a1 and a2) ,and CLSM images of the top 45°view (b1 and b2) of the electrospun 3D ultrafine fibrous zein scaffolds, Weight loss of electrospun 3D ultrafine fibrous zein scaffolds crosslinked with glutaraldehyde (GTA) and oxidized sucrose (OS) (c), Growth of preosteoblast cells on electrospun 3D ultrafine fibrous zein scaffolds crosslinked with OS and GTA(d), Spreading of MC3T3 cells on electrospun 3D ultrafine fibrous zein scaffolds crosslinked with OS and GTA(e1 and e2) (Liu, 2015).

5 APPLICATION OF ZEIN FILMS

The preparation of zein film is relatively easy, and it can be obtained by solution casting and extrusion (Zhang, 2015). Zein is dissolved in water and organic solvents, and dried at room temperature or under specified conditions, and then through the hydrophobic interaction within the protein molecule., hydrogen bonds, disulfide bonds, etc. work together to obtain a zein film (Krochta, 1994).

To verify the compatibility between zein films and cells, Jian Dong (Dong, 2004) prepared zein films for culturing human hepatocytes (HL-7702) and mouse fibroblasts (NIH3T3). The results show that there is no significant difference between zein film and Corning microplate cultured cells. This preliminary test shows that zein is a material with good biocompatibility, which can be used in the development of tissue engineering. Yi-Long Han (Han, 2014) obtained a zein film with a thickness of 50-100 μm by casting protein on a coverslip, and the obtained film had good transparency in a dry environment. In vitro experiments with NIH 3T3 cells showed that the film performed similarly to culture plates, and this material has potential applications in cell culture substrates and microfluidic devices. Figure 6. exhibits the preparation method of zein film.

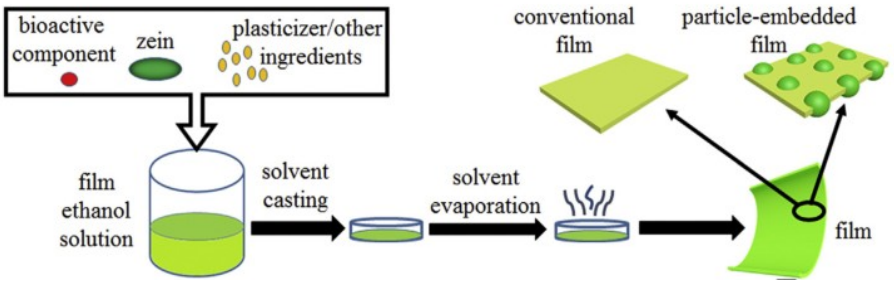

Figure 6: Preparation process of cast zein film (Han, 2014).

Bacterial infection on implanted devices is an important clinical problem and is associated with bacterial adhesion, bacterial proliferation, and biofilm formation. Traditional treatments include both systemic and topical antibiotic administration. However, the side effects caused by systemic

administration are greater, so topical administration has become an attractive means. Jian-Xi Fu et al. (Fu, 2009) prepared ciprofloxacin-loaded zein microspheres by a phase separation method, and then prepared zein microspheres containing the above-mentioned. The solution of microspheres was poured on the surface of a disc, and after the solvent evaporated, a zein microsphere film (CF-MS film) loaded with ciprofloxacin was obtained, and the antibiotic-loaded zein film maintained antibacterial activity for more than 6 days in experiments. The material has potential application value in the antibacterial of implanted devices.

6 CONCLUSION

Zein is an environmentally friendly and biocompatible material. The promotion of its industrial application contributes to the realization of carbon peaking and carbon neutralization, so it has been paid more and more attention by researchers. Making zein in the form of particles, fibers and films has been brilliant in the research fields of drug delivery, drug sustained release, tissue engineering scaffolds, etc. However, it should be noted that the current research is basically still in the preclinical stage, but we believe that through the continuous efforts of researchers, zein will step into practical clinical applications in the near future and benefit mankind.

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