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Synthesis and biological response of casein-based silica nano-composite film for drug delivery system

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ABSTRACT

Casein possesses many interesting properties that make it a good candidate for conventional and novel drug delivery systems. In this study, casein-based silica nano-composite was prepared via double in situ method, and the as-prepared latex particles were evaluated in terms of their morphology and size through transmission electron microscopy (TEM). The film morphology was investigated by scanning electron microscopy (SEM) and energy dispersive X-ray (EDX), and the mechanical property and response behavior of the films as a function of silica content were discussed. Ibuprofen was used as the model drug. The drug load and release properties were studied by solid-state nuclear magnetic resonance (solid-state NMR), Fourier transform infrared (FT-IR), SEM and in vitro test. The composite latex particle showed a stable core–shell structure, and the film exhibited a regular surface with even SiO_2 distribution. The drug load efficiency of the composite films increased with adding silica because of the adsorption of the drugs on the silica. In an acidic release medium, the ibuprofen-loaded composite showed a slower drug release dependent on the silica content. These behaviors were most likely due to the reduced diffusion rate of the drug through the composite microsphere, which resulted from the interaction between the silica and the drug.

1. Introduction

Over the past decades, the use of biodegradable polymers for fabricating pharmaceuticals and biomedical agents has increased dramatically. The most important biomedical applications of biodegradable polymers are in the areas of controlled drug delivery systems [1,2]. With the increasing demands for safer drug carriers, natural polymers have attracted much attention because of their non-toxicity as drug delivery carriers [3].

Generally, proteins represent good raw materials because they have the advantages of excellent absorbability and low toxicity of the degradation end products [4]. According to the literature, a wide variety of protein-based delivery system formulations have been studied, including films [5], hydrogels [6], micro-particles [7–9] and nanoparticles [10,11].

As a natural protein, casein has attracted increasing attention to preparing biodegradable drug carriers. It is known that many of the structural and physicochemical properties of caseins facilitate their functionality in drug delivery systems [11]. These properties include the binding of ions and small molecules, the exceptional surface-active and stabilizing properties, excellent emulsification and self-assembly properties, superb gelation and water binding capacities. The pH-responsive gel swelling behavior renders casein useful for programmable release. In addition, casein has various shielding capabilities, which are essential for protecting sensitive and enables casein to control the bio-accessibility and promote its bioavailability. As we know, certain techniques have been employed to fabricate casein-based drug delivery systems in the forms of nanoparticles, micro-particles hydrogels and beads [4]. However, the current literature is extremely limited to the use of casein for the films for drug delivery. There were no reports investigating the use of this highly acceptable bio-polymer for tablet coating processes until Abu Diak et al. [12] assessed casein as a film former for tablet coating with the aid of different water soluble and insoluble plasticizers. In their study, diltiazem HCl core tablets were coated with casein using a pan coater and the efficacy of four different plasticizing agents (glycerol, triethyl citrate, dibutyl sebacate and oleic acid) in producing a continuous tablet coat was evaluated. Interestingly, only those films formed using oleic acid were capable of producing a continuous and acceptable coat.

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Acrylic-based polymers have been utilized for many years as extremely good film formers or coating agents in pharmacy because of their superior mechanical properties [13]. In our previous study, poly-acrylate film-forming materials were synthesized and the as-prepared films were proved to have excellent mechanical properties [14]. It is expected that the introduction of acrylate polymers into casein matrix can enhance the loading and releasing properties for drug delivery systems.

Recently, inorganic/organic hybrid materials have attracted increasing interest owing to their extraordinary thermal, mechanical, optical, magnetic and electrical properties [15–22]. Therefore, this kind of materials has potential applications in coatings, adhesives, electronics, catalysis, drug delivery, and diagnostics [23–28]. Among the various types of organic-inorganic composite, polymer-based nano-silica composite is considered to be a good candidate for the drug delivery system because of its superior properties including the higher thermal, mechanical strength, interface action and drug absorption [29–31]. In our former researches, silica was employed to improve the comprehensive properties of acrylic-based polymer films [32] and casein-based films [33,34].

This paper aims to fabricate polyacylate modified casein/silica nano-composite films for drug delivery system. In the fabrication process, polyacylate was generated via in situ polymerization from acrylate monomers and silica was generated via in situ hydrolysis from the precursor tetraethoxysilane (TEOS) in casein matrix. The effects of TEOS usage on the film morphology, film properties, drug load efficiency and drug release behavior were discussed. The drug releasing mechanism for the drug-loaded film was proposed.

2. Materials and methods

2.1. Materials

Casein was purchased from Zhejiang Huatian Ltd. Triethanolamine was supplied by Tianjin Fuyu Chemical Engineering Co., Ltd. Caprolactam (99.0% purity) was obtained from Shanghai Guoyao Chemical Reagents Co., Ltd. All the initiators (99.5% purity) were supplied by Tianjin Fuyu Chemical Engineering Co., Ltd. Butylacrylate (BA, 99.0% purity) and methyl methacrylate (MMA, 99.0% purity) were purchased from Tianjin Kemio Chemical Reagents Co., Ltd. Tetraethoxysilane (TEOS, 98.0% purity) was supplied by Tianjin Kemio Chemical Reagents Co., Ltd. Silane coupling agent (KH570, 98.0% purity) was obtained from Nanjing Liangui Chemical Reagents Co., Ltd. Tetrahydrofuran (THF, 98.0% purity) was purchased from Tianjin Bodi Chemical Co., Ltd. Ibuprofen (CAS grade, 99.0% purity) was supplied by Chengdu Beisite Reagents Co., Ltd. Dialysis bag (the pore size 14,000 Da) was purchased from Baijuyi Biological mall. Buffers of pH 2.0 (hydrochloric acid/potassium chloride), pH 6.8 (sodium dihydrogen phosphate/disodium hydrogen phosphate) and pH 10 (hydroxide/boracic acid/potassium chloride) were prepared in double distilled water. The raw materials for buffers (99.5% purity) were purchased from Tianjin Hongyan Reagents Co., Ltd.

2.2. Synthesis of casein-based latex emulsion

Casein-based silica composite latex was prepared via emulsifier-free polymerization as follows. First, 21.0 g of casein was added to 5.25 g of triethanolamine dissolved in 100 mL of distilled deionized water in a 250 mL three necked round-bottom flask fitted with a digital electric stirrer, a reflux condenser, a thermometer and a constant pressure dropping funnel. This solution was kept stirring for 2 h under $65 \pm 2\,^{\circ}C$. After the reaction mixture was heated up to $75 \pm 2\,^{\circ}C$, 3.0 g of caprolactam dissolved in 12 mL of distilled deionized water and 4.7 mL of TEOS was drop wise added to the system at a speed of 2 drops per second. Thirty minutes after TEOS was exhausted, 1.3 mL of silane coupling agent was drop wise added into the system. The reaction lasted for 4 h before 3.0 g of BA, and 1.0 g of MMA were added in the system, and then the reaction was allowed to keep stirring for 0.5 h. Then, 0.09 g of 25% (w/w) initiator solution was drop wise added through a constant pressure dropping funnel at a speed of one drop per second. After 2 h of polymerization at $75 \pm 2\,^{\circ}C$, modified casein emulsion was obtained.

2.3. Fabrication of ibuprofen-loaded casein-based film

The composite films before drug-loading were prepared by casting the latex emulsion on the stainless glass petri dish. This was followed by an additional 4 h of drying at room temperature. Then, the films were peeled off and stored in a desiccator. The Ibuprofen loaded casein-based films were fabricated according to the following process. Firstly, ibuprofen particles (M) were dispersed into THF solvent solution, and the ibuprofen dispersion was obtained. Then the dried composite films (M_0) were immersed into the ibuprofen dispersion for drug absorption. Lastly, the films were taken out and the ibuprofen-loaded casein-based film was obtained after THF evaporation at 50 °C in a vacuum oven for 5 h (M_1). The drug loading efficiency was calculated according to the following formula:

$$\text{Loading efficiency}(\%) = \frac{M_1 - M_0}{M} \times 100$$

2.4. Analysis of latex particle and film morphology

Solid-state ^{13}CNMR measurement was conducted on an Infinity-plus 400 MHz NMR equipment (Varian, USA). The morphology of latex particles was investigated by an H-800 transmission electron microscope (Hitachi, Japan) operated with an acceleration voltage of 75 kV. Before tested, the samples were diluted with distilled water and stained with 2% phosphotungstic acid solution. The mean particle diameter and particle size distribution (PDI) were determined using a Nano-ZS (Malvern, UK) based on static light scattering. The chemical structure of the latex particles was determined by an IR Prestige-21 FTIR spectrometer (Shimadzu, Japan) in the spectra range of 4000–400 cm^{-1} using the KBr pellet method. TG experiments were carried out on a Q500 TG thermogravimetric analyzer (TA, USA) with a heating rate of 20 °C min^{-1} from 35 °C to 600 °C in the air atmosphere. SEM analysis was performed on a S4800 SEM instrument (Hitachi, Japan). Before tested, casein-based films of about 3 mm thickness were freezing fractured, and the top surfaces and cross-sections were both coated with a thin layer of gold using a vacuum sputter at an acceleration voltage of 5 kV. EDX was performed on an EDAX 32 system simultaneously. Mechanical properties including tensile strength and elongation at break of the films were measured using an AI-3000 universal testing machine (Gotech, China) following the standard ISO 3376-1976 and the standard GB/T 4689 22-1996. Prior to the analysis of the mechanical properties of the films, they must be conditioned under standard atmospheric conditions for 24 h.

2.5. Swelling behavior in response to pH

The role of pH on the water absorption rate of polymeric films is of great importance since a change in pH of the medium often causes a fluctuation in free volumes accessible to penetrating water molecules, and it affects swelling properties of polymers [35]. The pre-weighed samples were packed in dialysis bags and immersed in buffers of pH 2, pH 6.8 and pH 10. The bags were removed at regular intervals, and the surface water was removed by filter paper