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Sodium caseinate-magnesium aluminum silicate nanocomposite films for modified-release tablets

Wanassnant Kajthunyakarn, Duangkamon Sakloetsakun, Thaned Pongjanyakul*

Division of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen 40002, Thailand

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ABSTRACT

The aim of this study was to investigate the effect of clay, magnesium aluminum silicate (MAS), on the properties of sodium caseinate (SC) dispersions and films. Moreover, the SC-MAS dispersions were evaluated for film coating of modified-release tablets. The results showed that MAS addition led to particle flocculation and viscosity synergism in the SC-MAS dispersions. Exfoliated or intercalated nanocomposites of the SC-MAS films could be formed because of the molecular interaction of both components via hydrogen bonding. The puncture strength and elongation of the dry SC films decreased with increasing MAS ratios. However, MAS added enhanced the puncture strength of the wet films and reduced drug permeability and diffusivity across the films in acidic medium because of lower water uptake and denser matrix structure of the films. The SC-MAS dispersions showed strong potential for use as a film coating material with few defects in the coated acetaminophen (ACT) tablets. The ACT release of the coated tablets in acidic medium was modified by varying the MAS ratios and film coating levels. In addition, the SC-MAS coated tablets possessed sustained-release behavior for the drug under simulated gastrointestinal conditions. This finding indicates that the SC-MAS nanocomposite films can be applied as a tablet coating material to modify drug release.

1. Introduction

Thin film technology is highly important in pharmaceutical manufacturing, being employed in, for example, film coatings for masking an unpleasant taste and odor of drugs and for sustaining drug release in tablets [1]. The films loaded with drugs have been used as drug delivery systems [2]. Furthermore, the application of thin films is extended to the food industry, where the films are developed and used for food packaging and wrapping. Natural polymers have been widely employed for these purposes because of their biocompatibility and biodegradability. Polysaccharides, such as chitosan, have been used as tablet film coatings [3] and food packaging [4]. In addition, protein-based films, which were prepared from gelatins [5] and caseins [6], have been applied as a packaging material. Moreover, casein film coatings for fruits show a minimum loss of weight and juice level during storage under ambient conditions [7].

Caseins, biomacromolecules from milk, are composed of 94% protein and 6% colloidal calcium phosphate [8]. Caseins' molecular weights are in the range of 19 and 25 kDa. The average isoelectric point of caseins is approximately 4.6 to 4.8. Caseins in an acidic form (casein salt) have a low aqueous solubility, but sodium caseinate (SC), the sodium salt of casein, is freely soluble in water, except when the pH is close to the isoelectric point [9]. Because SCs have distinct hydrophobic and hydrophilic domains, self-assembly into stable micellar structures in aqueous solutions can occur when their concentrations are higher than the critical micelle concentration, 1.0 mg mL^{-1} [10]. Because of this characteristic, SCs are used as emulsifying and foaming agents in the food industry. Furthermore, SCs have been applied in the pharmaceutical industry as a solubilizing agent for poorly soluble drugs [11,12]. SCs also have a potential use as drug delivery systems, particularly hydrogels [13], beads [14], microparticles [15,16] and nanoparticles [17,18].

One of the crucial properties of SC is to act as a film forming agent. SC can be used for tablet film coatings [9,19] and food packaging [6]. Unfortunately, the SC films have several disadvantages, including their mechanical properties and water vapor permeability [20]. Therefore, it is necessary to modify the film properties of SC by adding plasticizers such as glycerin and sorbitol [21,22], cross-linking agents, such as aldehydes [22,23], and water insoluble additives, such as fatty acids and wax [24], and celluloses [25]. Among these modifiers, the addition of water-insoluble substances is the interesting approach to modify physicochemical, mechanical, and permeability properties of the SC films. From the literature reviews, clays could potentially be used to modify the polymeric film properties and molecular interaction between

* Corresponding author.
E-mail address: thaned@kku.ac.th (T. Pongjanyakul).

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polymers, and clay can create a new type of films called nanocomposite materials [26–28]. Thus, it is interesting that incorporation of clays may improve the SC film properties for use as a pharmaceutical film coating.

Montmorillonite clay (magnesium aluminum silicate (MAS)), is employed as a pharmaceutical excipient due to its non-toxicity and non-irritation at levels used in drug formulations [29]. MAS is composed of many silicate layers, where each silicate layer consists of a central octahedral sheet of aluminum or magnesium and two external silica tetrahedron layers [30]. The silicate layers of MAS can be separated when hydrated with water, and the silanol groups (-SiOH) on the surface of the silicate layers show a negative charge that brings about a strong electrostatic interaction with a positively charged substances, such as drugs [31], proteins [32], and polymers [33]. Moreover, the silanol groups can interact with anionic polymers such as xanthan gum [34], carbomer [35], and sodium alginate [36,37] via hydrogen bonding. Molecular interaction of polymeric molecules and MAS may create two types of nanocomposites [30]. The first type is an exfoliated nanocomposite in which the silicate layers of MAS can be completely dispersed in the polymer matrix. The latter type is an intercalated nanocomposite in which the space between two silicate layers of MAS can be occupied by polymeric molecules. The formation of nanocomposites has a significant influence on the key properties of the films, resulting in decreased water absorption, swelling and drug permeability compared to native polymeric films [26].

Therefore, the aims of this work were to prepare and investigate the SC films with MAS incorporated for use in tablet film coating. The composite dispersions with various SC-MAS ratios were prepared using simple mixing. The particle size and zeta potential of the dispersed phase, as well as the viscosity of the dispersions, was determined before film casting. Film properties, such as thermal behavior, crystallinity, mechanical properties, water uptake and erosion, and water vapor and drug permeability were characterized. Molecular interaction and nanocomposite formation between SC and MAS were also examined. Additionally, the SC-MAS dispersions were evaluated as a tablet film coating material that acetaminophen (ACT) was used as a model drug in this study. Film morphology, water uptake and ACT release of the coated tablets were investigated, as well.

2. Materials and methods

2.1. Materials

SC (sodium salt from bovine milk) and MAS in granular form (Veegum® HV) were purchased from Sigma-Aldrich Company (St. Louis, MO) and R.T. Vanderbilt Company, Inc. (Norwalk, CT), respectively. Glycerin and ACT were obtained from Namsiang Co., Ltd. (Bangkok, Thailand) and Pharma Thai Co., Ltd. (Bangkok, Thailand), respectively. Spray-dried lactose (Flowlac®100, Thai Meochems Co., Ltd., Bangkok, Thailand), microcrystalline cellulose (Ceolus® PH102, SiamChem-Pharm (1997) Co., Ltd., Bangkok, Thailand), magnesium stearate (Mallinckrodt, Inc., USA), and colloidal silicon dioxide (Aerosil® 200, Degussa, Japan) were used for preparing core tablets. All other reagents were of analytical grade and were used as received.

2.2. Preparation of SC-MAS dispersion

SC (5 g) was dispersed in 80 mL of distilled water. MAS (0, 0.25, 0.5, or 1 g) was dispersed in hot water (10 mL). Next, the MAS dispersion was mixed with the SC dispersion to obtain SC-MAS ratios of 1:0, 1:0.05, 1:0.1, or 1:0.2 by weight, respectively. The pH of the SC and SC-MAS dispersions was adjusted to 6.8 using 0.1 M HCl or 0.1 M NaOH because pH of the dispersion affected ionization of SC [38] and zeta potential of MAS [39]. All dispersions were adjusted to the final volume (100 mL) using distilled water prior to testing. Additionally, MAS dispersion (1% w/v) at pH 6.8 was also prepared and examined for comparison.

2.3. Characterization of SC-MAS dispersion

2.3.1. Particle size determination

The particle size of the MAS and SC-MAS dispersions was measured by using a laser diffraction particle size analyzer (Mastersizer2000 Model Hydro2000SM, Malvern Instruments, Ltd., UK). The samples were dispersed in 70 mL of distilled water in a sample dispersion unit and stirred at a rate of 50 Hz for 30 s before measurement. The volume weighted mean diameters were determined and reported.

2.3.2. Zeta potential measurement

The zeta potential of the dispersions was measured using a laser Doppler electrophoresis analyzer (Zetasizer Model ZEN 2600, Malvern Instrument Ltd., UK). The temperature of the samples was controlled at 25 °C. The dispersions were diluted to obtain appropriate concentrations (count rates > 20,000 counts s^{-1}) prior to the measurements.

2.3.3. Viscosity determination

The viscosity of the dispersions was determined using a Brookfield digital rheometer (Model DV-III, Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA). The small sample adaptor with spindle no. 31 was used. The temperature of the dispersions was controlled at 35.0 ± 1.0 °C. The single point viscosity of the dispersions at a shear rate of 20.40 s^{-1} was reported.

2.4. Preparation of SC-MAS films

SC and SC-MAS films were prepared by using a casting/solvent evaporation method. SC (5 g) was dispersed in 80 mL of distilled water, and glycerin (30% w/w based on SC content) used as a plasticizer was added into the SC dispersion. MAS (0, 0.25, 0.5, 1, or 2.5 g) was dispersed in hot water (10 mL), and the MAS dispersion was mixed with the SC dispersion to obtain the SC-MAS ratios of 1:0, 1:0.05, 1:0.1, 1:0.2, or 1:0.5 by weight, respectively. The pH of the SC and SC-MAS dispersions was adjusted to 6.8 using 0.1 M HCl or 0.1 M NaOH. All dispersions were adjusted to the final volume (100 mL) using distilled water and stirred for 30 min at room temperature (27 ± 2 °C). Then, 20 mL of the SC and SC-MAS dispersions was cast onto a plastic mold (6.0 cm × 9.5 cm) and dried at 60 °C for 24 h. The dry films were peeled off and kept in desiccators prior to characterization.

2.5. Characterization of SC-MAS films

2.5.1. Thickness determination

Thickness of the dry and wet films was measured at different places using a microprocessor coating thickness gauge (Minitest600B, ElektroPhysik, Germany). The dry films were cut and placed on a control plate. The probe, which had been connected to the measurement gauge and calibrated using a standard film, gently moved downward to touch the film, and the film thickness was subsequently measured. To determine the film thickness in the wet state, the films were subsequently placed in a small beaker containing 0.1 M HCl or pH 6.8 phosphate buffer, which was shaken occasionally in a water bath at 37.0 ± 0.5 °C for 5 min. The samples were taken and blotted to remove excess water. The thickness of the wet films was immediately determined following the procedure mentioned above.

2.5.2. SEM and DSC studies

Surface and film matrix morphologies of the films were observed by scanning electron microscopy (SEM). The films and cross-sections of films were mounted onto stubs, coated with gold in a vacuum evaporator, and investigated using a scanning electron microscope (Hitachi S-3000N, Tokyo, Japan). The thermal behavior of the films was investigated using differential scanning calorimetry (DSC). The DSC