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Use of cassava starch nanocrystals to make a robust rupturable pulsatile release pellet

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ABSTRACT

This study aimed to investigate cassava starch nanocrystals as a filler in rupturable ethylcellulose film to fabricate a more robust system for pulsatile delivery. The rupturable pulsatile release pellets consisting of a drug (theophylline) layered core, a swelling layer (croscarmellose sodium) and a rupturable layer of ethylcellulose with cassava starch nanocrystals were developed. The effects of amount of cassava starch nanocrystals, coating levels of swellable and rupturable layers on lag time and drug release were investigated. The results revealed that cassava starch nanocrystal decreased puncture strength and elongation at break of ethylcellulose film. Lag time of the pulsatile pellets was increased with increasing levels of swellable and rupturable coatings, whereas increasing amount of cassava starch nanocrystals decreased lag time and lowered sensitivity of lag time on the rupturable coating level. Additionally, increasing level of swellable layer and amount of cassava starch nanocrystals led to rapid drug release after lag time whereas higher level of rupturable layer caused a slower drug release. In conclusion, cassava starch nanocrystals could lower the mechanical properties of the ethylcellulose film and lower sensitivity of lag time on the rupturable coating level, providing the robust pulsatile release system with rapid drug release after lag time.

1. Introduction

Humans exhibit circadian rhythms in their pathphysiology according to the master clock of body [1]. Therefore, chronopharmacotherapy of diseases namely, arthritis, nocturnal asthma, peptic ulcers, allergic rhinitis, myocardial infarction needs drugs with pulsatile release patterns, i.e., complete and rapid drug release to properly maintain the disease state. Oral pulsatile drug delivery systems are designed for application at optimal time against diseases that occur depending on circadian rhythm. Most of pulsatile drug delivery systems are reservoir systems with a barrier layer. The barrier can be dissolved or eroded after a predetermining lag time, and drug is released outside from reservoir system [1,2]. The time controlled explosion system which is another reservoir-type pulsatile drug delivery system is easier to manufacture and provides drug release rapidly after rupturing of the surrounding membrane. The rupturing of the barrier layer is achieved by the expansion of drug containing core due to the water uptake through rupturable barrier layer. Generally, the lag time prior to drug release from a reservoir type device can be prolonged with increasing membrane thickness [3]. Ethylcellulose (EC) is a frequently used polymer as rupturable coating of pulsatile delivery system, because of its water insolubility, semi-permeability, adjustable water permeability and mechanical properties [4]. It is a brittle material with sufficient strength to withstand mechanical stress after a certain period of time. Using only EC as the rupturable layer could not provide a robust formulation for pulsatile release system due to the high sensitivity of the lag time on the EC coating level [5]. Modifications of EC film including composite polymer blends have been reported in rupturable pulsatile release system. The use of EC composite with other polymers can offer major advantages, including: (i) adjusting of desired drug release patterns, (ii) improving film formation and storage stability, (iii) developing site specific drug delivery within the gastrointestinal tract (e.g., colon targeting) [6,7]. Addition of some materials such as magnesium stearate [5] or talc [8] in EC film was able to develop a less sensitive and more robust formulation.

Starch nanocrystals are crystalline platelets prepared by the disruption of the semi-crystalline structure of starch granules through the acid hydrolysis of amorphous parts. The morphology of starch

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nanocrystals appeared to be in relation to the crystalline structure of original starches. Different types of starch nanocrystals were obtained with a thickness ranging between 4 and 8 nm and a diameter from about 50 to 120 nm depending on the source [9]. Starch nanocrystals have been used as a reinforcement filler in various polymeric composites [10]. For the most cases, the incorporation of starch nanocrystals resulted in an increase in both tensile strength and elastic modulus of the composite films but a decrease in elongation at break. To dates, there are no reports on utilization of starch nanocrystals in polymeric films for pharmaceuticals. As the nanocrystals are derived from starch which is widely used pharmaceutical excipients, it would be applicable for pharmaceuticals in the future.

In this study, starch nanocrystals derived from acid hydrolysis of cassava starch was used to modify the properties of rupturable film for pulsatile delivery system. As cassava starch is abundantly available in Thailand and other developing countries, an inexpensive material for pharmaceutical industry is expected. The objective of this study was to fabricate more robust formulation for pulsatile release system by incorporation of cassava starch nanocrystals (CSN) as a filler in rupturable ethylcellulose film. The physical and mechanical properties of EC-CSN composite films were characterized. The pellets with consecutive layers of a drug layered core, a swelling layer and a rupturable layer (EC-CSN) were developed. The effects of amount of CSN, and coating levels of swellable and rupturable layers on lag time and drug release from the pulsatile release pellets were investigated.

2. Materials and methods

2.1. Materials

Cassava starch nanocrystal (CSN) was prepared by sulfuric acid hydrolysis of cassava starch according to the method of Li et al. [11]. The CSN was provided by National Nanotechnology Center, National Science and Technology Development Agency (NSTDA), Thailand. The platelets of CSN were in the range of 12–24 nm by using Transmission Electron Microscopy (JEM-ARM200F, JEOL, Japan). Sugar sphere 1000–1190 μm, (IPS, Milan, Italy), theophylline anhydrous (Labscan Asia, China), ethylcellulose NF (Ethocel ™ 10 Premium, Dow Chemical, Midland, MI, USA), hydroxypropyl methylcellulose (Methocel™ E15, Dow Chemical, Midland, MI, USA), Povidone K90 (BASF, Ludwigshafen, Germany), croscarmellose sodium (CCS) (ND-2HS, Nichirin Chemical Industries, Hyogo, Japan), dibutyl sebacate NF (DBS) (Morflex, Greensboro, NC, USA), magnesium stearate (Peter Greven, Venlo, Netherlands) were used as received. All of other materials are of pharmaceutical grade.

2.2. Preparation of free films

Free films of EC and EC-CSN composites with different weight ratios of EC to CSN (100:0, 90:10, 85:15, 80:20 and 75:25), plasticized with 10% w/w DBS based on polymer weight, were prepared with regard to 13.2% w/w solid content. Both polymers were dissolved in ethanol for 6 h and further mixed with 10% w/w DBS for 30 min. Then, 25 g of ethanolic polymer solution was casted on a leveled Teflon sheets (14 cm × 14 cm) and dried for 24 h at 15 °C under special cover to control solvent evaporation in order to attain the homogeneous films. The dried films were peeled off and incubated in the oven at 50 °C for 12 h. After that, the films were cut into 6.5 cm × 6.7 cm test sections and were kept in a desiccator containing a saturated aqueous magnesium nitrate solution (55% RH) at 25 ± 0.5 °C for 2 days before testing. The thickness of dry films was determined in five positions with a thickness gauge (Minitest 600, Erichsen, Hemer, Germany).

2.3. Evaluation of free films

2.3.1. Mechanical properties of free films

Mechanical properties of the free films of EC and EC-CSN composite were determined in the dry and wet states by texture analyzer (TA.XT. plus, Stable Micro Systems, UK). The film specimens were mounted on a film holder (n = 6). The puncture probe (spherical end: 5 mm diameter) was fixed on the load cell (5 kg), and driven downward with a crosshead speed of 0.1 mm/s to the center of the film holder's hole. For the wet state, the film samples mounted with the film holder were immersed in 0.1 N HCl at 37 °C for 1 h prior to performing the puncture test. Force-displacement curve was recorded until the film was ruptured. The puncture strength and %elongation at break were determined from the force-displacement curve and calculated as described previously [4,5,8].

2.3.2. Water uptake of free films

Water uptake of the free films in 0.1 N HCl was determined by gravimetric method. The test was conducted as follows: pieces of films, 1 cm × 2 cm, were weighed and placed into disintegration apparatus (Hanson QC21, CA, USA) filled with 0.1 N HCl, followed by vertical shaking (30 rpm) at 37 °C. At predetermined time points, samples were withdrawn, carefully blotted with a tissue paper to remove surface water, the films were accurately weighed (Wt) and dried to constant weight at 50 °C (Wd). The water uptake (%) at time t was calculated as follows:

$$water\ uptake\ (\%) = \frac{(Wt - Wd)}{Wd} \times 100$$

2.3.3. Water vapor permeability of free films

Disks were punched from the free films and placed on open 30 mL glass vials containing 12.5 g of activated silica gel beads. Then, the vials were held in place with lids having an 11.3 mm diameter of test area (1.003 cm^2). After that, the vials were placed in a desiccator containing silica gel for 12 h and then placed in a desiccator containing saturated sodium chloride solution (75% RH). The desiccator was kept in a chamber at 25 ± 0.5 °C. The weight changes were recorded periodically at 0, 2, 8, 12, 24 and 72 h. The water vapor permeation (WVP) rate was obtained from the slope of the relationship between amount of water permeated and time. The water vapor permeability coefficient (WVPC) of the free films was calculated using the following equation.

$$WVPC = \frac{Mh}{A\Delta P_v}$$

Where M is the WVP rate, h is the mean thickness of the free film, A is the area of the exposed film, and ΔP_v is the vapor pressure difference.

2.4. Preparation of pulsatile release pellets

2.4.1. Drug layering on sugar seeds

Theophylline (15% w/v) was dispersed in ethanol/water (60:40 w/w) mixture containing HPMC (6% w/v) and the dispersion was stirred until clear dispersion was obtained. Then this dispersion was layered on the pre-warmed sugar seeds in a fluidized bed bottom spray coater equipped with a Wurster insert (GPC 1.1, Glatt, Germany) until 20% (w/w) weight gain was achieved. The process conditions were as follows; batch size: 1000 g; inlet temperature: 48–50 °C; product temperature: 38–40 °C; air flow: 80 m^3/h; nozzle diameter: 1.2 mm; atomizing air pressure: 2.5 bar; spray rate: 10 g/min. The drug layering pellets were further dried in the coating pan for 15 min at 60 °C after the coating process was finished.

2.4.2. Coating for swellable layer

A swelling agent, croscarmellose sodium (CCS) (20% w/v) was layered onto the drug layer using Povidone K90 (6% w/v) as a binder.