Development of a Zein-Based System for Colon Specific Delivery

Minh Ngoc-Uyen Nguyen, Toi Vo Van, Phuong Ha-Lien Tran, and Thao Truong-Dinh Tran

Abstract

Zein was investigated in this study as a coating material for colon specific delivery of prednisolone. To strengthen the ability of film layer in the protection of a dosage form, Kollicoat® MAE 100P was investigated together with zein in an appropriate ratio. Interactions between these materials were evaluated by Fourier Transform Infrared spectroscopy (FTIR). Through the simulated gastrointestinal (GI) environment, the coated tablets released drug immediately after passing the intestinal medium. Zein was proved to be a potential coating material for a delayed release of drug to colon. FTIR spectra indicated that zein and Kollicoat® MAE 100P had only physical interactions at different ratios. Various parameters should be critically controlled in the preparation process to achieve the colon drug delivery. This work may contribute to new applications of zein for attempts of pharmaceutical scientists to design oral controlled drug release dosage forms.

Keywords

Colon specific delivery • Zein • Film coating

1 Introduction

Drug delivery target to colon has lately developed as an advantageous approach to delivery drug for both systemic and local treatments [1]. Despite the high concentration of microorganism and their not well-known effect on drug metabolism, the environment in colon is less hostile to many drugs in comparison to the stomach and small intestine [2]. Prodrugs, enzyme-triggered release systems, pH-controlled release systems and time controlled release systems are major approaches for colon specific drug delivery [3–6].

The most commonly utilized system for site-specific delivery is pH-sensitive film coating. Normally, tablets would be double or triple layers coated to protect the active agent on the way to large intestine. Many studies also combined two or more of coating copolymers in order to reach the high quality performance of the film coating [7–9]. The drawback of this method is time-consuming and requires a lot of workloads due to the design of multi-layer coating and thick film applied. Henceforth, development of a new strategy to effectively transport drug to the lower part of the GI tract, protect the active agent form digestive enzymes as well as reduce coating time and the number of layers is very crucial.

Zein—a biopolymer that is extracted from corn—has advantages of excipients favorable in pharmaceutical applications. It has been applied in controlled delivery of essential oils, dyes or anti-cancer drugs and gene delivery as micro/nanoparticles, etc [10]. Zein can also be soluble at high pH value (>11) or with the presence of anionic surfactants. Although zein has been recently used in food industry as a coating material, there has not been such a

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T. Vo Van et al. (eds.), *6th International Conference on the Development of Biomedical Engineering in Vietnam (BME6)*, IFMBE Proceedings 63, https://doi.org/10.1007/978-981-10-4361-1_85

study of zein as a coating material for colon specific drug delivery systems.

2 Materials and Methodology

2.1 Materials

Prednisolone (PRL) was supplied by Tianjin Tianyao Pharmaceuticals Co., Ltd (China). Zein was purchased from Acros Organics™ (New Jersey, USA). Kollicoat® MAE 100P was supplied by BASF chemical company (Ludwigshafen, Germany). Polyethylene glycol (PEG 6000) was obtained from Sino-Japan chemical (Taiwan). PEARLITOL® Mannitol was purchased from Roquette Pharma Company (France). Magnesium stearate was purchased from Nitika Pharmaceutical Specialities Pvt. Ltd (India). Hydrochloric acid (HCl) and Sodium chloride (NaCl) were supplied by Xilong Chemical Co., Ltd (Shantou, Guangdong, China). Sodium acetate (CH_3COONa) was kindly gifted by Korea United Pharm Inc. (South Korea). Ethanol, Sodium hydroxide (NaOH), Disodium hydrogen phosphate dodecahydrate ($Na_2HPO_4.12H_2O$), Potassium dihydrophosphate (KH_2PO_4) and Acetic acid (CH_3COOH) were provided by Guangdong Guanghua Sci-Tech Co., Ltd (Shantou, Guangdong, China). Methanol for high performance liquid chromatography (HPLC) was purchased from Fisher Scientific (Pittsburgh, Pennsylvania, USA). All chemicals and reagents were used without further purification.

2.2 Preparation of Coating Solution

A mixture of ethanol and purified water (ratio 60:40 v/v) was chosen as the solvent for preparation of coating solution. Zein and Kollicoat® were separately dissolved in a sufficient amount of the solvent. The plasticizer for this solution—PEG 600—was dissolved in another beaker with the same solvent before adding to Kollicoat® solution. These coating components were then homogenously mixed together under magnetic stirrer. Zein solution and Kollicoat® solution were also prepared and evaluated as the controls for the modified formulations. Details of formulation compositions are showed in Table 1.

2.3 Preparation of Coated Tablets for Colon Delivery

At first, SD sample (Zein:PRL = 2:1.3) was mixed with mannitol and magnesium stearate in succession to form homogeneous mixture of PRL equivalent to 5 mg dose. Then, this mixture was directly compressed into core tablets, whose hardness slightly varied from 62 to 72 N, by a single punch-press machine (TDP 1.5, China) at 8 mm-diameter.

The tablets were then coated by a 2–4 kg/batch pan coater (BYC-400, Taiwan), whose atomization pressure was 1.04 kg/cm^2 (20 Psi), flow rate was 2 rpm, rotating speed was 12 rpm and the inner air flow temperature was constantly at 40 °C. Coating was thoroughly done until the increment of tablets average weight reached 8% (C1–C4 formulations) compared to the core tablets' average weight. Finally, coated tablets were dried out by hot air at 50 °C in 15 min and were kept in a closed lid container.

2.4 In-vitro Drug Release Studies for Specific Colon Drug Delivery System

Dissolution Tester (Pharma Test, PT-DT70, Germany) with USP apparatus I (Basket method, 75 rpm, 37 ± 0.5 °C) was critically used to study drug release profiles at pH 1.2, 6.8 and 7.4 [9]. HPLC analysis then was used to measure the amount of PRL released.

2.5 HPLC Analysis

Concentration of Prednisolone (PRL) was measured by HPLC instrument (Dionex Ultimate 3000 HPLC, Thermoscientific Inc., USA) at Luna 5 µ C18 analytical column (150 mm × 4.6 mm). The standard setting included: mobile phase—methanol and deionized water 60:40 (v/v) ratio, flow rate—1.2 mL/min; the running time—5.5 min. The

Table 1 Composition of coating solutions

No.	Ratio	Zein (g)	Kollicoat® (g)	PEG 6000 (g)	EtOH (mL)	% coating layer
C1	10:0	62.5	–	6.25	1000	8 ± 0.5%
C2	0:10	–	62.5	6.25	1000	8 ± 0.5%
C3	5:5	31.25	31.25	6.25	1000	
C4	4:6	25	37.5	6.25	1000	8 ± 0.5%
C5	4:6	25	37.5	6.25	1000	5 ± 0.5%

wavelength to analyze column effluent in UV detector was 254 nm.

2.6 Molecular Interaction (FTIR)

A FTIR spectrophotometer (Bruker Vertex 70, Germany) provided spectra for investigation of zein and coated formulations. All samples were scanned from 500 to 4000 cm^{-1} with resolution of 2 cm^{-1}.

3 Results and Discussion

3.1 Dissolution Studies

The quality of coating layer was investigated by two main elements: ratios between zein and Kollicoat® in coating solution and thickness of the film on core tablets. The experiment found out that zein and Kollicoat® at ratio 5:5 (C3) was not well compatible. Its solution appeared precipitation of zein particles slowly at the bottom of the beaker when stopping stirring. In contrast, ratio 4:6 of zein and Kollicoat® performed an excellent homogenous mixture with no agglomeration. Hence, the ratio 4:6 was chosen for the coating process to provide a uniform coated layer on core tablets and prevent nozzle from obstruction during film spraying.

The drug release profiles from coated tablets with the combination of zein and Kollicoat® MAE 100P (C4) and with each component alone as controls (C1 and C2) were presented in Fig. 1. As a sole coating material in the formulation, zein showed it weak ability of film formation since it could not totally coat the core tables. As a result, immediate release of PRL was observed at pH 1.2 with C1 formulation. The dissolution rate constantly increased until reaching 95% of PRL at pH 7.4—colon stimulated fluid. The phenomenon demonstrated the weak mechanical strength of zein as film forming material for colon delivery system. The similar assumption was also reported by a study of A.N. Zelikin about polymer thin film [11]. On the other hand, the release profile from Kollicoat® coated sample confirmed its ability of low pH resistance. The coating layer with Kollicoat® protected the core tablets for 4 h through pH 1.2 and pH 4.6 until reaching the medium of pH 6.8. The active agent immediately released about 80% during the time at pH 6.8 due to the absence of protective shield. This result was predictable as Kollicoat® is commonly used for small intestine delivery. Therefore, the combination between zein and Kollicoat® would satisfy the requisite of delivery drug to colon. Kollicoat® could increase the weak mechanical strength of zein as mentioned above as well as zein would enhance the resistance of Kollicoat® to higher pH value.

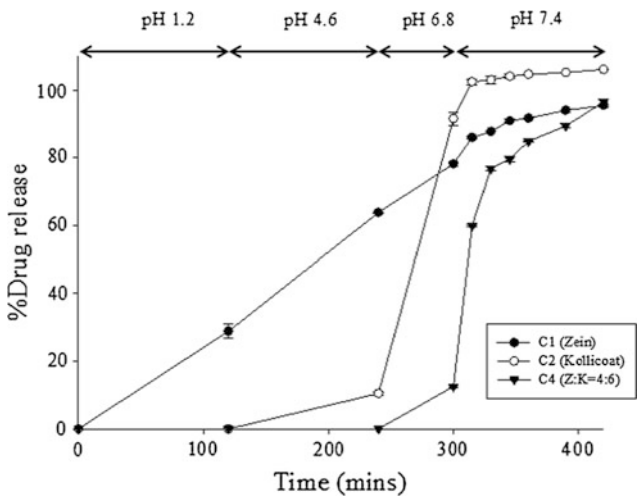

Fig. 1 Dissolution profile of PRL from coated tablets of C1, C2 and C4 as a function of time in order of different pH media

With the combination of zein and Kollicoat® at ratio 4:6, the thickness of coating film was analyzed to choose the most appropriate one from the two values of percentage of average weight gain of the ratio 4:6 formulations. Coated tablets at 5 and 8% weight gain (C4 and C5, respectively) were evaluated by dissolution test. The dissolution profile from C5 is not showed on Fig. 1 as it performed a non-uniform film coating on tablets' surfaces, leading to different release rates from each individual tablet of the same batch. For the drug release profile from C4, it was clearly seen in the coating of 8% weight gain, the core tablets were protected until they reached the final medium at pH 7.4—simulated for colonic fluid. Though drug still released at pH 6.8 at a certain level, the study has proved that zein plays a crucial role in combination with Kollicoat® and presents an effective shield to avoid the release of drug on the way to the large intestine.

3.2 Physicochemical Characterization of Coating Layer

FTIR spectra of zein and the mixture of Zein and Kollicoat® MAE 100P of coating solutions were carried out (Fig. 2). From Kollicoat®-PEG 6000 sample, the spectrum illustrates the characteristic peaks combining from both Kollicoat® and PEG 6000. Besides, zein FTIR spectrum presented two amide bands at 1655 and 1539 cm^{-1}, and an O-H stretch at 3418 cm^{-1} [12]. As clearly seen from the graph, C4 spectrum performed a new two-teeth peak appears from 1655 to 1735 cm^{-1}. It would be considered that this peak was formed as the combined peaks at the same wavenumbers from pure zein and Kollicoat®-PEG 6000. Hence, there was

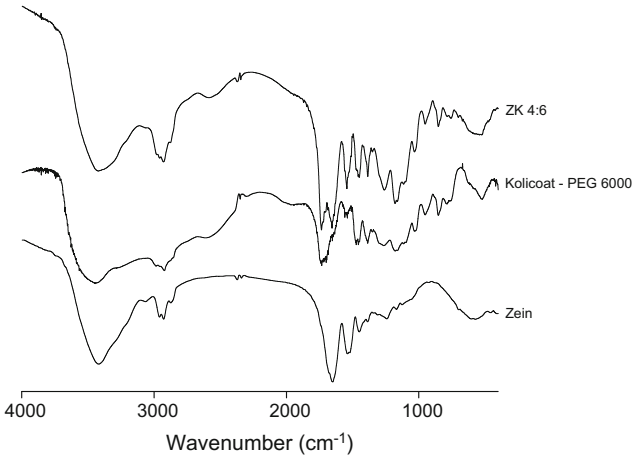

Fig. 2 FTIR spectra of Zein and different coating solutions

no such a chemical reaction occurring between zein and Kollicoat® in the coating solution.

4 Conclusions

The study has suggested that it is potential to apply zein as coating material for colon specific drug delivery system. The combination of zein and Kollicoat® MAE 100P could create an effective protective film to carry an anti-inflammatory drug (PRL) to the colon in GI tract. Effectiveness of this coating film was also found to be predominantly influence by weight ratio of different components in the coating formulations and the thickness of the coating layer. FTIR spectroscopy confirmed the absence of a chemical reaction between zein and Kollicoat®.

Acknowledgements This research is partially funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 106-YS.05-2015.02. We also thank to International University and Vietnam National University—Ho Chi Minh City for supporting to our research activities.

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