International Journal of Pharmaceutics 370 (2009) 81–86

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

A novel zein-based dry coating tablet design for zero-order release

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ARTICLE INFO

Article history:
Received 7 July 2008
Received in revised form 28 October 2008
Accepted 17 November 2008
Available online 3 December 2008

Keywords:
Zein
MCC
Starch
Dry-coated tablet
Zero-order release

ABSTRACT

The purpose of this study was to design zero-order release of dry-coated tablets using pure zein powder, zein granule and zein blend containing two common pharmaceutical excipients such as microcrystalline cellulose (MCC) or starch in different proportions as coating material. The 5-fluorouracil (5-FU) was used as a model drug. The physical characterization and drug release behaviors of dry-coated tablets were investigated. The surface structure of the tablets was examined by a scanning electron microscopy. The correlation coefficient (R) was used as indicator of the best fitting of the zero-order model for drug release. It was found that zein formed a gelatinous layer fast and its network prevented disintegration of the tablet during dissolution process. Zein-based dry coating tablets had good physical properties such as compactibility and friability. All formulations fit the zero-order model well. The mechanism for zero-order release of these dry-coated tablets was solvent penetration into the dosage form and dissolving the drug, the dissolving core formed an apex in the center of the tablets and the drug diffused out. The apex of zein-coated tablets worked as orifice of an osmotic system and released the drug in zero-order profile.

1. Introduction

In the recent years of development in pharmaceutics, increasing attention is being given for administering drugs in a more challenging and controlled manner for better therapeutic end point (Langer, 1998; Venkatraman et al., 2005). To achieve this, various controlled release dosage forms have been developed or are still under development in treating diseases because of their advantages over other conventional dosage forms (Torchilin, 2001; Mohhammed et al., 2004; Freiberg and Zhu, 2004). A goal in the design of an oral controlled release drug delivery system includes maintaining relatively constant therapeutic blood levels of the drug for a desired period. The osmotic drug delivery system among others achieves this (Liu et al., 2000). A dry-coated tablet is one candidate to deliver a drug in a controlled manner (Moussa and Cartilier, 1997; Lin et al., 2001).

Zein is an alcohol soluble protein of corn origin that exhibits hydrophobic properties, and a low water uptake. Consequently, zein has been used as a film former for controlled release of APIs in pharmaceutical tablets (Oshlack et al., 1994), and for masking the taste of bitter orally administered drugs (Meyer and Mazer, 1997). To date, zein has been widely studied as a film former (Park and Chinnan, 1995; Beck et al., 1996; Parris et al., 1997; Weller et al., 1998), all of those studies mentioned above were related to organic solvent-based films. Pharmaceutical coating technology has been shifting from organic solvent-based systems to aqueous systems, which are advantageous from the view points of environmental pollution, safety and cost. Existing aqueous-based coating materials include cellulosic and acrylic polymers. Examples of commercially available cellulosic aqueous coating systems are Aquacoat® from FMC Corp., and Surelease® from Colorcon Inc. Although both type of polymers have good film-forming properties resulting in tough protective coatings, there have been several problems confronted such as unexpected interactions with the active compound, tackiness of the polymeric films causing agglomeration during coating, cracking tendency in case of wrong coating composition or brittleness preventing coherent film formation (McGinity, 1997; Tarvainen et al., 2002, 2004). Due to these reasons, there is an ongoing research for developing novel coating materials or curing studies on the existing coating polymers. Zein and starch were investigated as coating materials and applied to tablets and pellets with regard to these attempts (O'Donnell et al., 1997; Palviainen et al., 2001; Krogars et al., 2002; Guo et al., 2008). Aqueous pseudolatex of zein has been applied to polymer films coatings for solid dosage forms (O'Donnell et al., 1997). However, aqueous coating systems are not always applicable. The dry coating technique was proved to provide both bead and tablet products giving sufficient gastric resistance, with a substantial reduction of processing time, in commercially available coating machines with minor modifications (Obara et al., 1999). Dry coating could be achieved by compression (Sawada et al., 2004; Sundy and Danckwerts, 2004), dry powder layering (Cerea et al., 2004) and hot-melt extrusion (Sauer et al., 2007; Andrews et al., 2008). Until now, there was no study about zein as a dry coating material in the literature.

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0378-5173/$ – see front matter © 2009 Published by Elsevier B.V.
doi:10.1016/j.ijpharm.2008.11.026

Table 1
The composition of coating and physical properties of the zein-coated tablets.

Formulation	Composition of coating layer	Mean weight (mg) ± S.D., $n = 20$	Thickness (mm) ± S.D., $n = 6$	Crushing strength (MPa) ± S.D., $n = 6$	Friability (%)
1	Zein powder	283 ± 3.96	3.54 ± 0.02	0.64 ± 0.04	0.73
2	Zein granule	282 ± 2.70	3.36 ± 0.03	0.61 ± 0.03	0.34
3	Zein:MCC 3:1	284 ± 5.05	3.20 ± 0.01	0.61 ± 0.05	0.50
4	Zein:MCC 6:1	283 ± 5.54	3.30 ± 0.02	0.51 ± 0.03	0.56
5	Zein:MCC 9:1	284 ± 4.08	3.88 ± 0.03	0.78 ± 0.11	0.55
6	Zein:starch 3:1	283 ± 4.36	3.81 ± 0.02	0.34 ± 0.12	1.25
7	Zein:starch 6:1	287 ± 5.03	3.86 ± 0.01	0.49 ± 0.06	0.82
8	Zein:starch 9:1	283 ± 6.61	3.44 ± 0.04	0.60 ± 0.07	0.79

The purpose of this study was to design zero-order release dry-coated tablets by using pure zein (zein powder or zein granule) and zein blends containing two common pharmaceutical excipients such as microcrystalline cellulose (MCC) and starch in different proportion as coating materials. The 5-fluorouracil (5-FU) was used as a model drug. The physical properties and drug release behaviors of dry-coated tablets were investigated. The uptake and eroding of dry-coated tablets in vitro study was also determined. The possible mechanism for zero-order release of this dry-coated tablet was proposed.

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used as received: 5-FU (Qilu Pharmaceutical Co., Shandong), zein powder (Bache Pharmaceutical Co., Wujiang), microcrystalline cellulose and starch (Ahua Pharmaceutical Co., Shandong).

2.2. Preparation of dry-coated tablets

Zein granule was prepared using wet granulation method. Aqueous preparation of starch (10%) was used as granulating agent. Zein powder manually mixed with MCC or starch in different proportions (Table 1). The dry-coated tablets were prepared by using a single-punch press (Shandong Medical Ltd., Shandong) under constant pressure and speed. About 80 mg quantity of 5-FU granules was directly compacted into a core tablet (6 mm in diameter). About half quantity of zein-based coating materials was first filled into a die having a diameter of 10 mm, then the core tablet was manually placed in the center of the coating materials. The remaining half quantity of coating material was then poured into the die and compressed the dry-coated tablet. The size of dry-coated tablet was determined by using a digital caliper (Wuxi, Jiangsu).

2.3. Physical characterization of dry-coated tablets

The dry-coated tablets were characterized for weight variation, thickness, crushing strength and friability. The crushing strength of each tablet was then measured using a hardness tester (78X-2, Shanghai). The friability was measured using a friabilator (CJY-300B, Shanghai). After weighing, 24 tablets from each batch were rotated for 100 revolutions and re-weighed to test for the percentage loss of weight.

2.4. Scanning electron microscopy

The surface structure of the tablets was examined by a scanning electron microscope (S-520, Hitachi, Japan). Preparation of the samples was accomplished by placing the tablets on to a specimen holder. The samples were coated with gold using an ion coater (Eiko IB-3, Japan). Electron micrographs were obtained at an acceleration voltage of 26 kV.

2.5. In vitro dissolution study

Dissolution studies were conducted using dissolution apparatus (UV2102 PCS, UNICO, Shanghai) according to the USP method II in 900 mL of distilled water at 37 ± 0.2 °C and agitated at 100 rpm with 6 tablets per study. Samples of 5 ml were withdrawn with media replacement at regular intervals, filtered through 0.45 μm filters and assayed spectrophotometrically for 5-FU at its λ_{max} 266 nm.

Photographs of the tablets before dissolution and the tablets at certain dissolution time were captured using a camera (IXUS450, Japan) to obtain changes of the dry-coated tablets during dissolution by recording the top view of the tablets.

2.6. Uptake and erosion studies

The uptake and erosion studies were performed according to Efentakis et al. (2006). In general, the zein-coated tablets without drug were placed in dissolution vessels, containing 900 ml of distilled water under the temperature and stirring conditions described in the dissolution studies section above. The tablets were removed excess liquid and then weighed on an analytical balance (A & D Company, Limited, Tokyo, Japan). The wetted tablets were then dried in an oven at 60 °C, then cooled in a desiccator and weighed again. This procedure was repeated until constant weight was achieved (final dry weight). Three different tablets were measured for each time point and fresh tablets were used for each individual time point.

The extent of erosion (E) was determined from:

$$E(\%) = \frac{W_s - W_f}{W_s} \times 100$$

where W_s and W_f are the starting dry weight and final dry weight of the same dried and partially eroded tablet, respectively. The increase in weight (uptake) due to absorbed liquid (A) was calculated at each time point from:

$$A(\%) = \frac{W_w - W_f}{W_f} \times 100$$

where W_w is the mass of the wet tablet before drying.

2.7. Release drug data modeling

The suitability of zero-order equation, which is reported in the literature identify the mechanism for the drug release of each formulation. The data were evaluated according to the following equation:

Zero-order model (Donbrow and Samuelov, 1980):

$$\frac{M_t}{M_\infty} = Kt,$$

where M_t is the accumulated amount of drug released in time t, M_∞ is the accumulated amount of drug in time ∞, and K is the zero-order release constant.

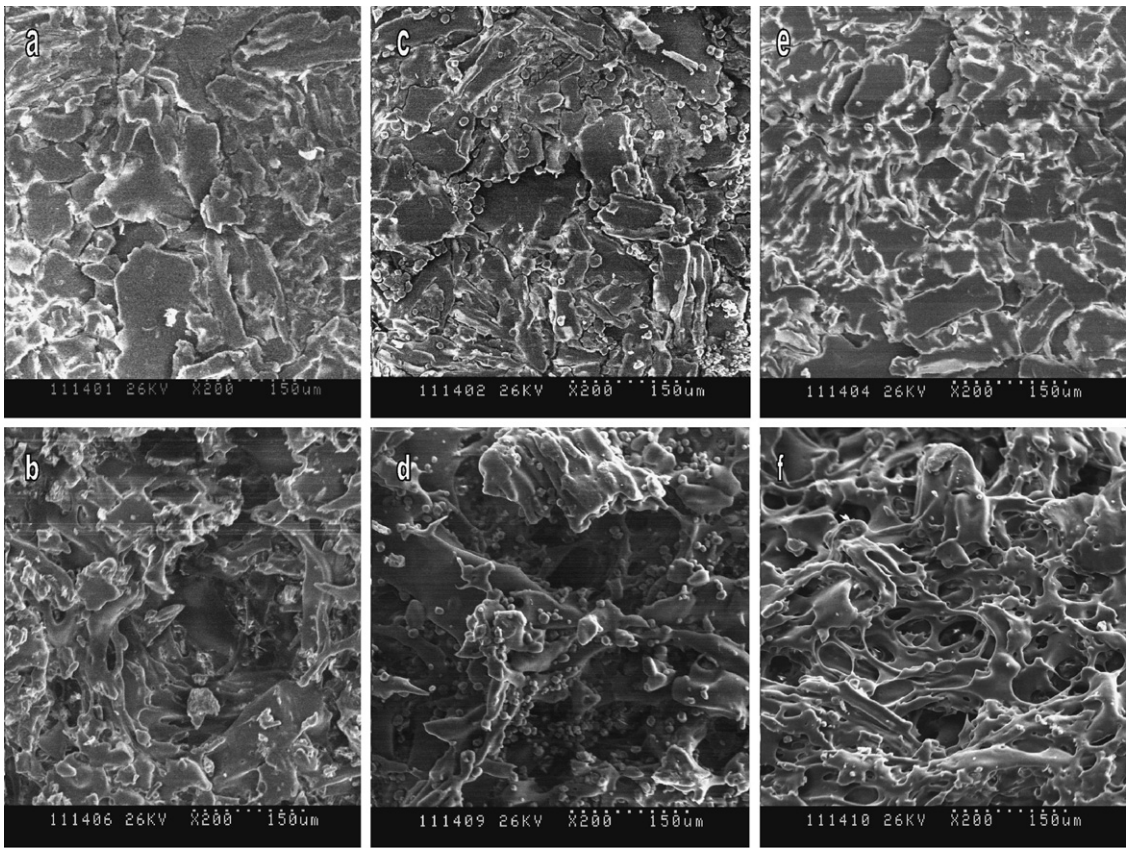

Fig. 1. SEM micrographs of zein-coated tablet surfaces. (Before and after dissolution: a and b, zein:MCC 6:1; c and d, zein:starch 6:1; e and f, pure zein.)

3. Results and discussion

3.1. Surface morphology of tablets

In order to study additives on the properties of zein-based dry coating tablet, the two common pharmaceutical excipients MCC and starch were, respectively, blended with zein in different portion (Table 1) for dry coating. The morphological evaluation of tablets is based on SEM micrographs. Fig. 1 showed the tablets made from zein:MCC (6:1) powder blend (Fig. 1a and b), zein:starch (6:1) powder blend (Fig. 1c and d) and pure zein powder (Fig. 1e and f) before and after dissolution, respectively. Before dissolution, the surfaces of tablet coated with zein:MCC or pure zein showed more compact (Fig. 1a and e) than the surface of tablet coated with zein:starch (Fig. 1c). After dissolution, the SEM images were taken from middle of the tablets. There is a significant difference in the microstructure of the tablets (Fig. 1b, d, and f). It is interesting that the gelatinous layer formed a network in the surface of tablet made from pure zein after dissolution (Fig. 1f). This could be due to disulphide-mediated polymerization of zein (Batterman-Azcona and Hamaker, 1998; Duodu et al., 2002). After dissolution, the interface of particles was obviously larger. The round starch particles were observed in the micrograph (Fig. 1d).

3.2. Physical properties of dry-coated tablets

Table 1 lists the physical properties (weight, thickness, crushing strength and friability) of the dry-coated tablets. Compared with the crushing strength of pure zein coated tablets, there were no big differences in crushing strength of the tablets coated either with zein:MCC 3:1 or zein:MCC 6:1. It was observed that higher portion of zein contained in the coating (zein:MCC 9:1) resulted in higher crushing strength of the tablets. However, when the coating contained starch, the crushing strength of the tablets was lower. It seems that the higher proportion of zein mixed with starch as coating material, the higher crushing strength was achieved (Table 1). The friability test showed that the less percentage loss of the tablets coated with zein granules than the tablets coated with zein powder. The tablets coated with zein:starch are more friable than the tablets coated with zein:MCC. The tablets coated with zein:starch (3:1) is the only one having a percentage loss more than 1%. From SEM images, it is obvious that there were some small starch particles in the tablet surface (Fig. 1c). It could be lost during friability test. Moreover, starch was not compacted well with zein. This is because of the poor compactibility of starch.

3.3. Drug release from dry-coated tablets

Fig. 2 is plot of the release rate of 5-FU from the tablets made from pure zein powder and zein granules in different coating thickness. The release performance of 5-FU from these dry-coated tablets exhibited different period of lag time. For the same core composition, decreasing the coating thickness or incorporating small amounts of other excipients (e.g. MCC or starch) in the coating shorten the release lag time and increase the release rate. This is similar to cross-linked amylose (CLA) dry-coated tablets (Moussa and Cartilier, 1997). It is obvious that the tablets coated with granules released more than the tablets coated with zein powder at the same thickness. It seemed that the porosity of outer coating layer prepared by different particle sizes (e.g. powder and granules) of zein seems to be responsible for this result. The smaller particle size of zein (e.g. powder) used the longer the lag time obtained. The similar result was also found in micronized ethylcellulose (EC) (Lin et al., 2001).

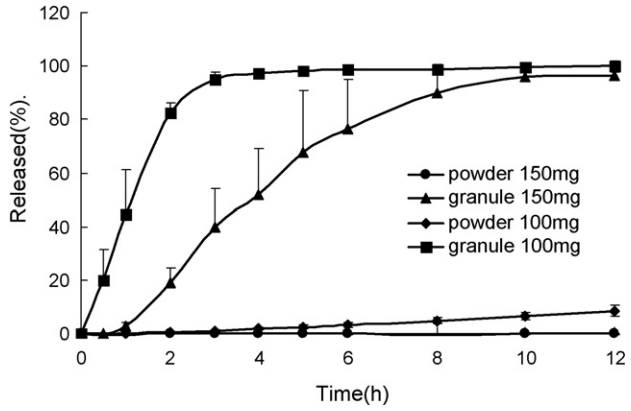

Fig. 2. The release rate of 5-FU from zein-coated tablets ($n = 6$).

Fig. 3 shows the release profiles of 5-FU tablets coated with zein blends of MCC (Fig. 3a) or starch (Fig. 3b) in different portion, respectively. These figures also show the contribution of each component in the release of the drug. The more portion of zein in the coating blend, the slower release rate of 5-FU was observed.

The results for the fitting of the zero-order model for 5-FU release from zein-based coating tablets are shown in Table 2. The correlation coefficient (R^2) was used as indicator of the best fitting for each of the formulation considered. All formulations except formulation 6 (zein:starch 3:1) fit the zero-order model well. SEM image showed that many separate starch particles in the surface of tablet which could be lost during dissolution (Fig. 1d). This could be the reason why drug release could not be controlled well. When more portion of zein in the formulation, the starch particles could exist in the network of zein particles during the dissolution. Therefore, the drug release could be better controlled. In the case of pure zein granule as coating material, zero-order release model fits well ($R^2 = 0.9953$) for 80% drug release. When zein:MCC (3:1) as coating material, the data ($R^2 = 0.9989$) was best fit to zero-order release model.

Table 2
Fitting of the zero-order model of drug release for zein-based coating tablets.

Formulation	K (zero-order release constant)	R^2 (correlation coefficient)
1	0.0076	0.9933
2	0.4135	0.9953
3	0.0569	0.9989
4	0.0463	0.9925
5	0.0394	0.9940
6	0.1847	0.9897
7	0.0542	0.9959
8	0.0370	0.9964

3.4. Uptake and erosion studies

The water uptake and erosion of the tablets in distilled water at various times are shown in Fig. 4. All zein-coated tablets gave a fast water uptake. After 30 min, the uptake of the tablets decreased (Fig. 4a). The tablets coated with pure zein showed slower water uptake with time than the other formulations. When more portion of zein contained in the coating formulation, the water uptake was slower after 7 h. It is clearly showed that the tablets containing starch had higher water uptake than the tablets containing

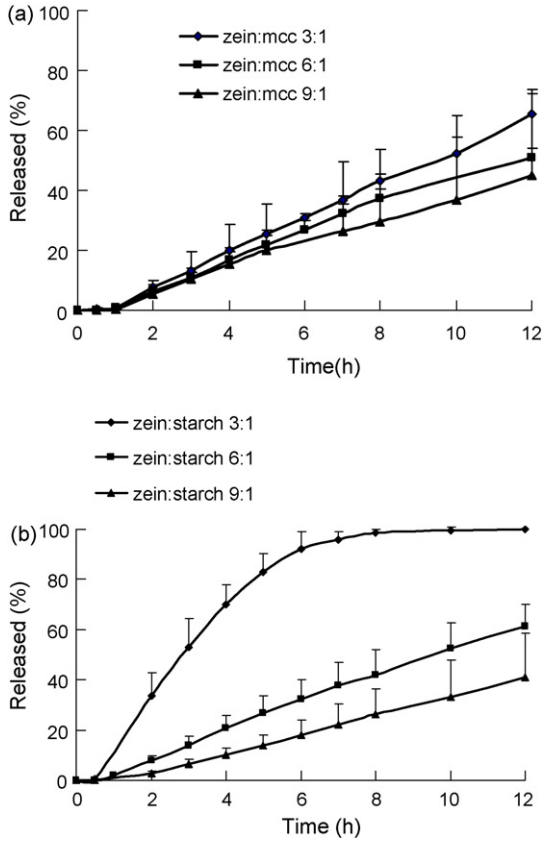

Fig. 3. The release rates of 5-FU from zein:MCC coated tablets (a) and zein:starch coated tablets (b) ($n = 6$).

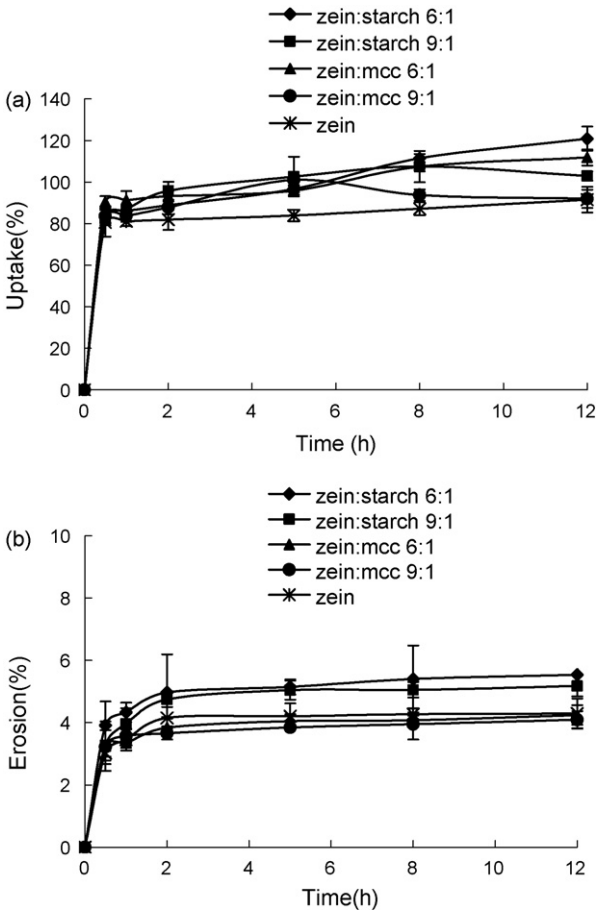

Fig. 4. Water uptake (a) and erosion (b) study of different formulations of dry-coated tablets ($n = 3$).

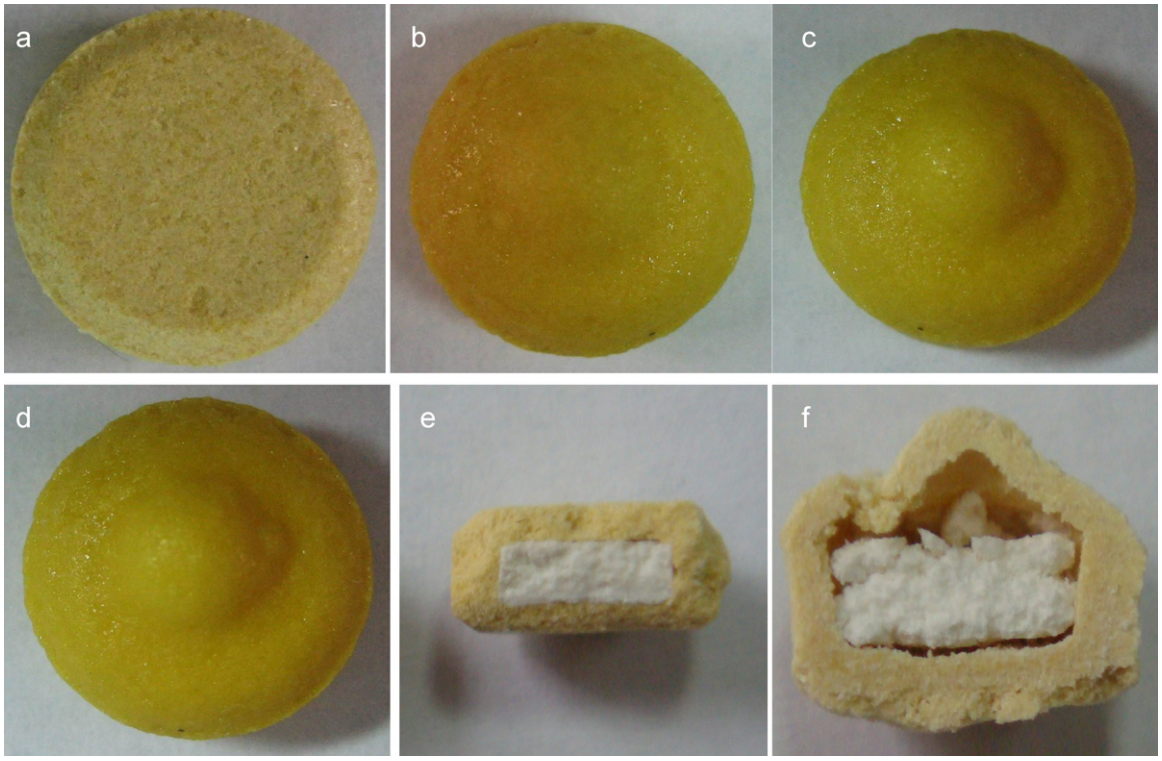

Fig. 5. The images of coated (zein:MCC 6:1) tablets at time of zero (a), 10 min (b), 2 h (c), 12 h dissolution (d) and cross-section images of the tablet before (e) and after dissolution (f).

MCC. The erosion of the tablets containing starch is higher than the tablets containing MCC (Fig. 4b). This is due to the poorer compactibility of tablets coated with zein:starch than the tablets coated with zein:MCC. However, the erosion of the coating tablets (Fig. 4b) was less obvious (less 5%) comparing with the water uptake of the coating tablets (Fig. 4a). The gel surface of zein with increased entanglement resulted in slower erosion. The similar phenomenon was also observed with sodium carboxymethyl cellulose (NaCMC) in a dry coating system (Efentakis et al., 2006). In aqueous polymeric coating systems, plasticizers in coating films could cause a change in water uptake, erosion and permeability of the films (Pongjanyakul and Puttipipatkhachorn, 2007).

3.5. Mechanism of drug release

It was found that zein could form gelatinous layer at 37 °C dissolution test (Figs. 1f and 5b–d). Zein forms a gelatinous layer fast and its network prevents the disintegration of the tablet during dissolution process. This is due to disulphide-mediated polymerization of zein (Batterman-Azcona and Hamaker, 1998; Duodu et al., 2002). From the water uptake and erosion studies, dissolution images in Fig. 5, it is evident that the drug released from the zein-coated tablets may involve three processes: solvent penetration into the dosage form, dissolving the drug and diffusion the drug out. It is interesting that the dissolving core formed an apex in the middle of the tablet after 10 min dissolution (Fig. 5b). At 12 h of the dissolution, the apex was still observed from the image (Fig. 5d). The cross-section images of the tablet before dissolution and after dissolution are shown in Fig. 5e and f. The apex and dissolving core could be seen in coated tablets after 12 h dissolution (Fig. 5f). This apex was observed for all formulation except the formulation 1 during dissolution study. Formulation 1 made from zein granules, there were more voids between particles. The drug could release from the voids. In the case of tablets made from zein powder and powder blend, under the compression force, the central part of coating tablet was thinner than the other part of the tablet. The dissolving core produced a force which formed an apex at the thinner part of tablet and diffused the drug out. The apex of zein-coated tablets worked like orifice of an osmotic system. Thus drug released in zero-order profile. Whereas in the case of ethylcellulose designing for dry-coated tablets, the loose packing of EC powders occurred in the middle of the lateral surface of dry-coated tablet, this loosely packed surface readily allowed solvent penetration and that finally caused the splitting of tablet shell into two halves in the dissolution medium (Lin et al., 2001). The solvent penetration should be the first step in the process of drug dissolution. The more portion of zein in the coating blend, the less penetration of solvent and slower dissolution of drug, lead to the delay of onset time of drug. In cross-linked amylose dry-coated tablets the delay of onset time of drug was also obvious. After this lag time, the drug release is linear for the range of constant thermodynamic activity in the core (Moussa and Cartilier, 1997). The release lag time could be shortened by an increase in the diffusion coefficient of the drug in the coating layer (e.g. adding excipients to the coating layer or increasing particle size of coating material), or a decrease in the coating thickness. In aqueous polymeric coating systems, the type of plasticizer used in polymer blends for the coating of solid dosage forms is of major importance for the resulting film coating properties and release kinetics (Lecomte et al., 2004).

4. Conclusions

The drug (e.g. 5-FU) yielded a zero-order drug release profile in distilled water using either the pure zein (powder or granule) and zein blend such as zein:MCC or zein:starch as dry coating materials. It was found that zein formed a gelatinous layer fast and prevent the disintegration of the tablet during dissolution process. Both particle size and proportion of zein in the coating blend could affect the physical properties (e.g. crushing strength and friability) and drug release rate of the tablets. The water uptake of coating tablets was

more obvious than the eroding of the tablets. The mechanism for zero-order release of zein-coated tablet was solvent penetration into the dosage form and dissolving the drug, the dissolving core formed an apex in the center of tablet and the drug diffused out. The apex of zein-coated tablets worked like orifice of an osmotic system and released the drug in zero-order profile.

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