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Enhanced oral bioavailability of novel mucoadhesive pellets containing valsartan prepared by a dry powder-coating technique

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ABSTRACT

The aim of this study was to develop novel mucoadhesive pellets containing valsartan (VAL) with enhanced oral bioavailability. Two types of VAL loaded core pellets were prepared by an extrusion/spheronization method, and further dry-coated with a mixture of hydroxypropylmethylcellulose (HPMC) and carbomer (CB) at different ratios. The effects of the pellet core composition, HPMC:CB ratio and coating level on the drug release from the coated pellets were investigated. The physicochemical properties of the core and coated pellets were characterized by scanning electron microscopy (SEM), X-ray diffraction (XRD), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR). In addition, the *in vitro* and *in vivo* mucoadhesion properties as well as the bioavailability of the coated pellets in rats were evaluated by using VAL suspension and core pellets as control preparations. The results of the release study demonstrated that the two types of core pellets, especially the pellets formulated with a solubilizer and a pH modulator gave considerably faster drug release than the VAL powder. However, the core and coated pellets exhibited similar release profiles indicating that the dry powder-coating did not retard the drug release. Strong molecular interactions were observed between the drug and the carriers in FT-IR analysis. The coated pellets displayed distinct mucoadhesive property *in vitro* and delayed gastrointestinal (GI) transit *in vivo*. Furthermore, the coated pellets exhibit significantly higher $AUC_{0-12\,h}$ and C_{max}, as compared to the core pellets and drug suspension. It was concluded that the mucoadhesive pellets could render poorly water soluble drugs like VAL with a rapid drug release, delayed GI transit and enhanced oral bioavailability.

1. Introduction

Oral drug delivery is the simplest and easiest way of administering drugs. However, the majority of new chemical entities (NCEs) display very poor aqueous solubility, resulting in low oral bioavailability due to insufficient dissolution throughout the gastrointestinal (GI) tract (Kesisoglou et al., 2007; Zhang et al., 2010). Especially for poorly soluble, highly permeable (BCS Class II) drugs, the rate of oral absorption is often controlled by the dissolution rate in the GI tract (Lobenberg and Amidon, 2000; Tran et al., 2010a).

Over the years, numerous attempts have been made to improve the solubility and dissolution rate of poorly soluble drugs, with the purpose of obtaining a more rapid and complete absorption. The major formulation tools include the microencapsulation (Vogt et al., 2008), solid dispersion (Tran et al., 2010a,b, 2011), and inclusion complex (Cappello et al., 2006; Moribe et al., 2011; Pravin et al., 2009). Although these are the most promising techniques which have been shown to enhance the dissolution characteristics of drugs, several difficulties are faced in designing drug delivery systems for better absorption and enhanced bioavailability. One of the difficulties is the inability to retain the drug delivery systems in the desired region of the GI tract.

Mucoadhesive drug delivery systems can prolong the GI transit time of drugs through a closer contract with the GI membrane and improve the drug absorption, and thus ensuring its optimal bioavailability (Bernkop-Schnurch et al., 2004; Chary et al., 1999; Perioli et al., 2004). Recently, mucoadhesive pellets, which were dry-coated with bioadhesive polymers (Piao et al., 2009), are highlighted because most commercial coatings suffer from the problems such as the use of toxic organic solvents, high-energy consumption and aging phenomena during storage (Cao et al., 2004, 2008). Dry powder-coating technique can overcome several limitations, such as the problems of solution viscosity and spray nozzle clogging. Moreover, because of the absence of large amounts of

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solvents or water, the processing times are much shorter (Pearnchob and Bodmeier, 2003; Smikalla et al., 2011).

The strategy for designing mucoadhesives is based principally on the utilization of the polymers with suitable physicochemical properties, such as bioadhesive, viscous, hydrogen binding property, or hydrophobic interaction, biocompatibility, *etc.* (Perioli et al., 2011; Petrovic et al., 2009; Wang and Tang, 2008). To date, the application of HMPC or CB in pharmaceutical fields has been mainly focused on the development of extended release formulations by producing gel barriers of varying consistency (Ikinci et al., 2004; Llabot et al., 2002; Perioli et al., 2011; Petrovic et al., 2009; Wang and Tang, 2008). Fewer reports have been published on the application of these polymers for dry powder-coating to impart mucoadhesive function and rapid release to poorly soluble drugs. In this study, we chose hydroxypropylmethylcellulose (HPMC) and carbomer (CB) as mucoadhesive substances, because their mixtures could offer acceptable adhesion and biocompatibility properties.

Valsartan (VAL), a highly selective angiotensin II receptor antagonist (ARB), is a well-known antihypertensive agent (Cappello et al., 2006; Dina and Jafari, 2000). The absolute bioavailability of VAL is about 25% (10–35%). This low oral bioavailability is primarily due to its poor solubility in the acid milieu of the GI tract. To improve its oral bioavailability, many groups have attempted to formulate VAL into solid dispersions using various carriers such as methyl-β-cyclodextrin (Pravin et al., 2009), gelucire50/13 (Shrivastava et al., 2009), poloxamer (Ha et al., 2011; Park et al., 2010), HPMC/SLS (Yan et al., 2012). However, few groups considered to improve the retention time of VAL in its main absorption region, *i.e.* the upper GI tract (Tarur et al., 2008) using mucoadhesive polymers, and to improve the dissolution rate of VAL at the same time.

The aim of present study was to design and evaluate novel mucoadhesive pellets with rapid drug release and enhanced oral bioavailability for VAL. Two types of VAL loaded core pellets were prepared by an extrusion/spheronization method, and further dry-coated with a mixture of HPMC and CB at different ratios. The effects of the core composition, HPMC:CB ratio and coating level on the drug release from the coated pellets were investigated. The core and coated pellets were also characterized in terms of their physicochemical properties, *in vitro* and *in vivo* mucoadhesion properties as well as the oral bioavailability.

The rationale behind the study was that poloxamer 188 (solubilizer) and NaOH (pH modulator) could render an enhanced drug release to VAL, at the same time, the dry powder-coating with mucoadhesive polymers could impart strong mucoadhesion force to the pellets in GI tract. To the best of our knowledge, this is the first time that the mucoadhesive pellets with the rapid drug release profiles have been investigated.

2. Materials and methods

2.1. Materials

Valsartan (VAL) was obtained from EuraPharm Co. (Suwon, Korea). Microcrystalline cellulose (Avicel® PH 101) was purchased from AsahiKASEI Co. (Shanghai, China). Polyvinylpyrrolidone K30 (Povidone® K30) was supplied by BASF (Shanghai, China). Carbomer (CB, Carbopol® 934P NF, particle size: 2–7 μm) and Poloxamer 188 (Lutrol® F68) were kindly supplied by Chineway Pharmaceutical Tech. Co. (Shanghai, China). Hydroxypropylmethylcellulose (HPMC, Methocel K4 M, particle size: 150–220 μm) was supplied by Colorcon (Shanghai, China). Silicon dioxide (SiO_2) was purchased from Shanhe Pharmaceutical Excipients Co. (Anhui, China). Sodium hydroxide (NaOH) and Ethanol were purchased from Sinopharm Chemical Reagent Co. (Shanghai, China). All other chemicals were of reagent grade and used without further purification.

Table 1
Formulation compositions (g) of core pellets prepared by an extrusion/spheronization method.

Codes	VAL	Avicel® PH 101	Povidone® K30	Poloxamer 188	NaOH
F1	60	180	5	–	–
F2	60	200	5	15	6

Table 2
Compositions (g) of coating materials used in dry powder-coating.

Codes	HPMC	CB	SiO_2
C1	4	2	0.06
C2	3	3	0.06
C3	2	3	0.06

2.2. Preparation of core pellets

Two different types of core pellets (F1 and F2) were prepared by an extrusion/spheronization equipment (Model JBZ-300, Yilian Drug Research Institute, Liaoning, China). Formulation compositions of the core pellets are shown in Table 1. Initially, 60 g VAL and 180 g Avicel® PH 101 were blended in a V-mixer for 5 min and then sieved through stainless steel 80 mesh sieve. Fifty grams of Povidone® K-30 solution (10%, w/w) as a binder was then added slowly to the dry blends for preparing F1 core pellet. On the other hand, 60 g VAL, 15 g poloxamer, 6 g NaOH and 5 g Povidone® K-30 were dissolved in 240 mL of EtOH/water (1:1.4, v/v) solvent mixture, followed by adding slowly to 200 g of Avicel® PH 101 for preparing F2 core pellets. The resulting wet masses were passed through a single-screw type extruder fitted with a 1.0 mm screen from the hopper at a constant speed of 40 rpm, respectively. The extrudates were processed immediately with a spheronizer at the speed of 700 rpm for 10 min. The resulting core pellets were then dried at 50 °C in an oven for 24 h.

2.3. Size distribution of core pellets

The dried core pellets were then sieved using a sifter (Model 35-VSS-300, Kukje Sci., Seoul, Korea) that was equipped with a series of four Chinese standard stainless steel sieves (18, 24, 30 and 34 mesh). The pellets retained on each sieve were weighted and the size distribution of core pellets was calculated. The pellets between 24 and 30 mesh (850–500 μm) size were collected for the subsequent dry powder-coating.

2.4. Dry powder-coating of core pellets

The two core pellets were dry powder-coated in a spheronizer equipped with a spay nozzle and a feeding hopper. The wetting agent was supplied by a peristaltic pump and sprayed simultaneously through the nozzle (size: 0.5 mm) and the coating powder was introduced by a feeding hopper. A 70% of EtOH as a wetting agent was sprayed to wet the core pellets prior to starting the feeding of the polymer powders. A mixture of HPMC and CB was used as coating materials with SiO_2 as a lubricant to prevent agglomeration and sticking of the pellets during coating. The compositions of the coating materials used in the dry powder-coating are summarised in Table 2. The rotation speed of the spheronizer was 500 rpm, the flow rate of wetting agent was 1 mL/min, and the atomizing air pressure was 0.5–0.6 MPa in all cases. The resulting dry powder-coated pellets were further dried at 50 °C in an oven for 6 h.

2.5. Analysis of drug content

Around two gram of core or coated pellets was placed in a mortar, and then grinded into fine powder using a pestle. One hundred milligram of resulting powder was accurately weighed and dissolved in 100 mL of methanol. Five milliliter of above solution was then diluted to 100 mL, filtered through 0.45 μm Millipore filters. The VAL concentration in filtrate was determined by a high-performance liquid chromatography (HPLC) at 265 nm. The HPLC system was Shimazu LC-20ATVP (Japan) and a reverse-phased column (Phenomenex® C_{18}, 150 mm × 4.60 mm, 4 μm) was used. The mobile phase was an acetonitrile/water/acetic acid (60:40:0.1, v/v/v) mixture and the flow rate was 1.4 mL/min.

2.6. Scanning electron microscopy (SEM)

The surfaces and cross-sections of the core (F1 and F2) and coated (F1C3 and F2C3) pellets were examined by SEM, using a HITACHI model S-4700 Scanning Microscope (Hitachi, Japan) operated at 15KV. The sample was cross-sectioned using a microcutter after dipping the pellet in liquid nitrogen for 10 min and then coated with gold under an argon atmosphere using a JEOL JFC-1100 sputter coater (Jeol, Japan) for approximately 3 min.

2.7. Release characteristics

The release characteristics of VAL from the core or coated pellets were determined according to the USP dissolution II paddle method at a rotation speed of 50 rpm in 900 mL of simulated gastric (pH 1.2) and intestinal (pH 6.8) fluids at 37 ± 0.5 °C, using a D-800 LS dissolution tester (Tianjin University Radio Factory, China). The core of the coated pellets equivalent to 80 mg VAL was exposed to dissolution medium for 6 h. The dissolution samples (5 mL) were collected at given intervals and the same volume of fresh dissolution medium were replenished. The collected samples were filtered through 0.45 μm Millipore filters. The concentration of VAL in the dissolution samples was determined by a HPLC as described above.

2.8. X-ray diffraction (XRD)

X-ray diffraction patterns were obtained on a diffractometer (MERCURY CCD, Japan) using Cu-*K*a radiation at a voltage of 40 kV and a current of 50 mA. The samples, which included VAL, Avicel® PH 101, Povidone® K30, Poloxamer, NaOH and core pellet powders (F1 and F2), were scanned in increments of 0.02° from 5° to 60° (diffraction angle 2θ) at a rate of 1 s per step using a zero background sample holder.

2.9. Differential scanning calorimetry (DSC)

The thermal behavior of VAL, Avicel® PH 101, Povidone® K30, Poloxamer, NaOH and core pellet powders (F1 and F2) were analyzed using a differential scanning calorimeter (TA Instruments, Model 2010, USA). The samples, ranging from 0.3 to 0.6 g, were weighed in a standard open aluminum pan while an empty pan of the same type was used as a reference. The samples were heated from 25 to 200 °C at a heating rate of 10 °C/min with nitrogen as the purge gas.

2.10. Fourier transform infrared spectroscopy (FT-IR)

An FT-IR spectrophotometer (Model Excaliber Series UMA-500, Bio-Rad, USA) was used to record spectra of the samples, including VAL and core pellet powders (F1 and F2). KBr pellets were prepared by mixing 1 mg of the sample with 200 mg of KBr. The samples were scanned from 400 to 4000 cm^{-1} at a resolution of 2 cm^{-1}.

2.11. Swelling study

To understand the functional contribution of HPMC:CB ratio to the swelling of the powder-coated pellets, water uptake studies were performed with a modified method from our previously described method (Cao et al., 2005). Briefly, 320 mg of the core and coated pellets was weighted and gently immersed in 5 mL distilled water for 5 min. After removal of excess water, the swollen pellets were reweighted. Water uptake (%) was expressed as a percentage of the initial pellet weight.

2.12. In vitro mucoadhesion study

The mucoadhesive properties of the core and coated pellets were evaluated using a texture analyzer (Model CT3, Brookfield Co., USA) (Hagesaether et al., 2009; Piao et al., 2009). Mucin discs were manufactured by compression of mucin (250 mg) using an IR press with a 15 mm diameter and a compression force of 4 tons was applied. These were then horizontally attached to the lower and upper ends of the Texture Profile Analysis (TPA) probes using double-sided adhesive tape. One hundred and sixty milligram samples were swollen in pH 6.8 simulated intestinal fluid for 5 min and then placed on the lower mucin disc. The analytical probe containing the mucin disc was lowered onto the surface of each pellet and a downward force of 2 N was applied for 2 min to ensure intimate contact between the mucin disc and the sample. The probe was then moved up in a vertical direction at a constant speed of 0.1 mm/s and the peak force (F_{max}, g) required to detach the mucin disc from the surface of each formulation was determined from the resultant force *versus* time plot. All measurements were performed in quintuplicate for each formulation.

2.13. In vivo GI mucoadhesion study

In order to investigate the effect of the coated pellets on the mucoadhesion property in GI tract, twelve male Sprague-Dawley (SD) rats weighing 250–310 g were randomly divided into two groups, each containing six rats. The mini capsule (DJE-22-1, NATSUME, Japan) containing either the core (F2) or coated (F2C3) pellets was administered orally at a dose equivalent to 1.44 mg (VAL)/kg body weight using an intragastric capsule injector (DJE-22, NATSUME, Japan) to the fasted rats of each group. The rats were sacrificed at 6 h after administration of the capsules, and the stomachs and intestines were excised from the rats to observe the GI retention and transit state of the pellets. The regions (length) of pellets moved and retained in GI tract of each rat were measured and compared.

2.14. Bioavailability study

2.14.1. Animal study

Eighteen male SD rats weighing 290–350 g were randomly divided into three treatment groups, each containing six rats. The rats were fasted over 12 h prior to the experiments. A polyethylene cannula (inner diameter, 0.58 mm; outer diameter 0.96 mm; dural plastics) was surgically introduced into the left femoral artery of rat under ether anesthesia to obtain blood samples at the various sampling times. The VAL powder was suspended in the distilled water, and the resulting suspension was administered orally at a dose equivalent to 1.44 mg (VAL)/kg body weight using an oral sonde to one group. Meanwhile, the mini capsules containing core (F2) or coated (F2C3) pellets were also administered orally at the same dose using an intragastric capsule injector to other two groups, respectively. Approximately 0.3 mL heparinized blood samples were collected using an indwelling cannula at 0.15, 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h, and then centrifuged at 1500 × *g* for 10 min to

collect the plasma samples. The plasma samples were stored in a freezer at −40 °C until analyzed by HPLC.

2.14.2. Treatment of plasma samples

Twenty microliters butyl p-hydroxybenzoate (10 μg/mL) as an internal standard was added to 200 μL of each plasma sample and voltexed for 5 s. A hundred microliters hydrochloric acid and 1 mL of diethyl ether were added to the mixture and then agitated for 5 min using a vortex mixer. Thereafter, the mixture was centrifuged at 1500 × *g* for 10 min. The organic phase was transferred into a tube and evaporated under a gentle stream of nitrogen in a dry-thermo unit at room temperature. The residue was then reconstituted with 0.1 mL methyl alcohol and 20 μL of the resulting solution was injected into the HPLC system.

2.14.3. HPLC analysis

Chromatographic separation was performed at a flow rate of 1.0 mL/min, at a wavelength of 254 nm, using a Phenomenex C_{18} (4.6 × 150 mm, 5 μm) column. The column temperature was maintained at 35 °C. The mobile phase was methanol:10 mM phosphate buffer (70:30, v/v, pH 2.8).

2.14.4. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters of VAL were calculated using non-compartmental methods. The maximum plasma concentration (C_{max}) and the time to reach the C_{max} (T_{max}) were read directly from the plasma concentration–time profiles of VAL. The areas under the plasma concentration–time curve from zero to 12 h ($AUC_{0-12\,h}$) were calculated using the classical trapezoidal method.

All data are presented as mean ± standard deviation. The statistical significance of the differences was performed using an analysis of variance (ANOVA) test and a p value < 0.05 or 0.01 was considered significant.

3. Results and discussion

Extrusion/spheronization is the most commonly used method for pellet production. Use of suitable excipients and fillers can be made to produce pellets of desirable quality (Sinha et al., 2005). It has also been reported that the extrusion/spheronization method are the best for preparing homogenous and compact pellets with smooth surface, which containing relatively high dose of active compound (Cao et al., 2008). The preparation of compact pellets is prerequisite to prevent pellets crushing during dry power-coating process. In this study, the core pellets containing VAL were prepared by an extrusion/spheronization method. We prepared two types of core pellets (F1 and F2) without or with poloxamer 188 (solubilizer) and NaOH (pH modulator), respectively. The fraction of the core pellets with a 24–30 mesh size was over 80% with a narrow size distribution for both F1 and F2 as shown in Fig. 1. However, the fraction of 18–24 mesh size was significantly higher for F2 than F1. This was likely due to the additional binding property of poloxamer 188 during preparation of wet mass for F2. The 24–30 mesh fraction of pellets was used for the dry powder-coating.

Dry powder-coating technique directly attaches polymer particles onto the surface of a solid substrate without organic solvents and large volumes of water. Instead of using only a single polymer, blends of different macromolecules may render better mucoadhesive property as well as smooth coating process to pellets. CB is very cohesive powder which intends to agglomerate. In our preliminary study, it was failed to produce CB-coated pellets, because CB powder tended to agglomerate immediately with the core pellets and could not be evenly coated onto the surface of the core pellets. Furthermore, it showed poor flow property, causing very ununiform feeding of powder with fluctuations. For these reasons, a mixture of HPMC and CB was attempted in this study. In addition,

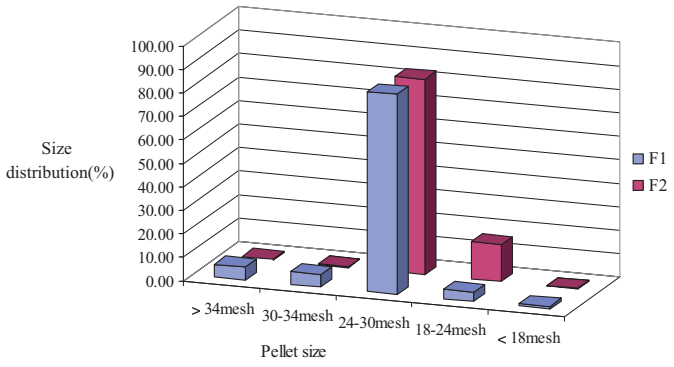

Fig. 1. Size distribution of core pellets (F1 and F2). F1 and F2 were the core pellets without or with poloxamer 188 and NaOH in core composition. Each value is the mean ± S.D. of three separate determinations.

1% of SiO_2 (w/w, %) was also incorporated to the mixture to improve the flowability of polymer powders. The dry powder-coated pellets were manufactured with different ratios (2:1, 1:1 and 1:2) of HPMC and CB using a spheronizer.

Table 3 shows the analysis result of VAL content in core and coated pellets. The drug content from different core and coated pellets was in the range of 97.57–103.34%, which indicated that formulation composition and preparing process had almost no effect on the drug content of pellets.

The surface morphologies and cross sections of the core pellets and coated pellets were observed by using a SEM and presented in Fig. 2. The surfaces of the core pellets (F1 and F2) were homogenous and smooth without any pores and cracks (Fig. 2A and E), while powder-coated pellets (F1C3 and F2C3) coated with a mixture of HPMC and CB at a ratio of 1:2 and a coating level of 15% showed rough and uneven surface (Fig. 2B and F). The coating powders were adhered to the surface of core pellet by the wetting agent during coating process. However, no distinct coating layers could be observed from the cross sections of the coated pellets when compared to the corresponding core pellets (Fig. 2C and D, G and H) under SEM.

Polymer coatings have been found to profoundly affect the dissolution behaviors of some drugs (Cao et al., 2004; Liu et al., 2009). In order to obtain highly mucoadhesive pellets with rapid drug release profiles, we investigated the effect of coating, especially HPMC:CB ratio and coating level on the release of the drug from the coated pellets. Meanwhile, the release patterns of the drug from the different types of core pellets (F1 and F2) were also compared.

Fig. 3 shows the effect of the ratio of HPMC to CB on the drug release from the coated pellets in a simulated intestinal (pH 6.8) fluid. The coated pellets with HPMC:CB ratio of 2:1 (F1C1), 1:1 (F1C2) and 1:2 (F1C3) exhibited similar release profiles. Moreover, the release curves of the core and coated pellets were almost identical, indicating that the coating layer did not retard the drug release from the core pellets. Similar results were also reported by another

Table 3
Content analysis of VAL in core and coated pellets.

Codes	Core pellets (%)	Coated pellets[a] (%)
F1	101.35 ± 4.46	–
F2	97.57 ± 2.49	–
F1C1	–	102.50 ± 2.11
F1C2	–	99.73 ± 3.87
F1C3	–	100.89 ± 2.06
F2C1	–	97.52 ± 2.10
F2C2	–	103.34 ± 2.48
F2C3	–	101.71 ± 3.27

[a] The coating levels of coated pellets were 15%. Each value represents the mean ± S.D. of three determinations.

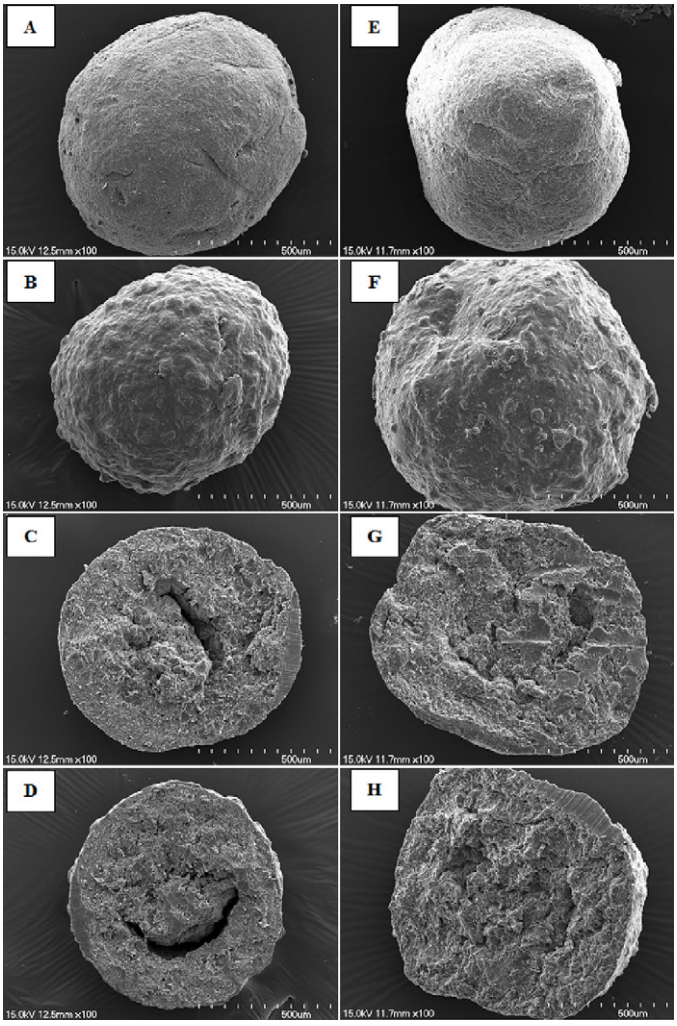

Fig. 2. Surface morphologies and cross sections of the core and powder-coated pellets by SEM. (A) Surface of core pellet (F1), (B) surface of coated pellet (F1C3), (C) cross section of core pellet (F1), (D) cross section of coated pellet (F1C3), (E) surface of core pellet (F2), (F) surface of coated pellet (F2C3), (G) cross section of core pellet (F2), (H) cross section of coated pellet (F2C3). F1 and F2 were the core pellets without or with poloxamer 188 and NaOH in core composition, respectively. Core pellets were coated with a mixture of HPMC and CB (1:2, w/w) and the coating level was 15%.

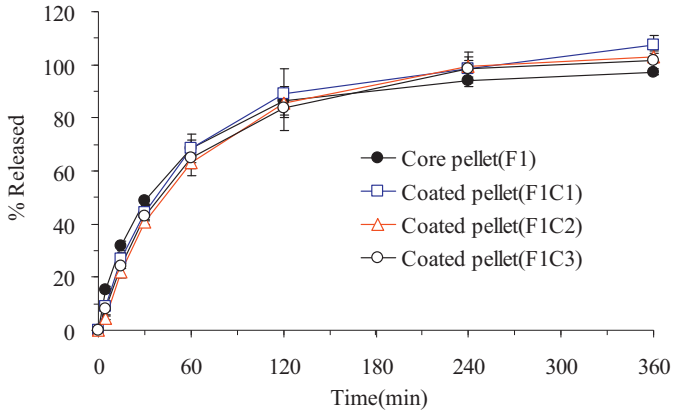

Fig. 3. Effect of HPMC:CB ratio on the drug release from coated pellets in simulated intestinal (pH 6.8) fluid. The weight ratios of HPMC to CB in coating layer were 2:1 (F1C1), 1:1 (F1C2) and 1:2 (F1C3), respectively. The coating level was 15%. Each data point represents the mean ± S.D. of three determinations.

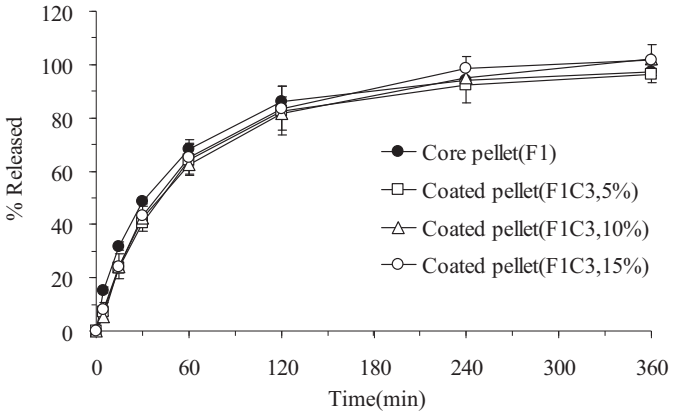

Fig. 4. Effect of coating level on the drug release from coated pellets (F1C3) in simulated intestinal (pH 6.8) fluid. The weight ratio of HPMC to CB in coating layer was 1:2 and the coating level were 5%, 10% and 15%, respectively. Each data point represents the mean ± S.D. of three determinations.

group *i.e.* powder-coating did not prolong the drug release (Piao et al., 2009).

In general, the amount of the coating is a critical factor controlling the drug release from dry powder-coated pellets (Pearnchob and Bodmeier, 2003). Hence, we compared the release of the coated pellets with different coating level at a range of 5–15%. The effect of the coating level on the drug release from the coated pellets (F1C3) is shown in Fig. 4. Interestingly, the drug release of the coated pellets did not alter as the coating level was increased, whereas the initial release was delayed when compared to that of the core pellets. It has been reported that plasticizer and curing time were key parameters influencing powder adhesion and coating compactness during dry powder-coating (Smikalla et al., 2011). Because both HPMC and CB have relatively high T_g values, a compact coating film was unlikely to be formed with absence of any plasticizers and lack of curing in the current coating process (Pearnchob and Bodmeier, 2003). It may explain why the HPMC:CB ratio and coating level did not retard the drug release in this study.

VAL is a weak acid, and therefore, has good solubility when pH > 5 and low solubility in acidic conditions. The release profiles of VAL from the core and coated pellets in simulated gastric fluid (pH 1.2) and intestinal fluids (pH 6.8) are shown in Fig. 5. The release rate of VAL from the coated pellets in different dissolution media was evaluated in comparison with those of the core pellets and VAL powder. In addition, the effect of core composition on the drug release was also investigated. As shown in Fig. 5, the release rates of VAL were significantly higher in pH 6.8 medium than pH 1.2 medium, in spite of the preparations. The core (F1 or F2) and coated pellets (F1C3 or F2C3) showed nearly identical release profiles in both pH 1.2 and pH 6.8 media as previously mentioned. Meanwhile, both F1 and F2 core pellets displayed significantly higher release rate compared to the drug powder, especially F2 showed the highest release rate among them. In pH 1.2 medium, due to the poor solubility of VAL, the dissolution of drug powder was very limited with less than 10% at 6 h. However, the release rate of F1 and F2 core pellets were significantly higher than the powder form, showing around 40% and 50% of the release at 6 h, respectively. At pH 6.8, the release rate of F1 core pellets was significantly higher than that of drug powder, reaching almost 100% at 4 h. Especially, drug release from F2 core pellets was dramatically improved with about 100% of drug release within 30 min. Thus, both the core and powder-coated pellets exhibited to improve the dissolution rate of the poorly water-soluble VAL in pH 1.2 and pH 6.8 media. These could be attributed to the drug carrier interaction during extrusion process, and further the solubilization and pH modulation effects by

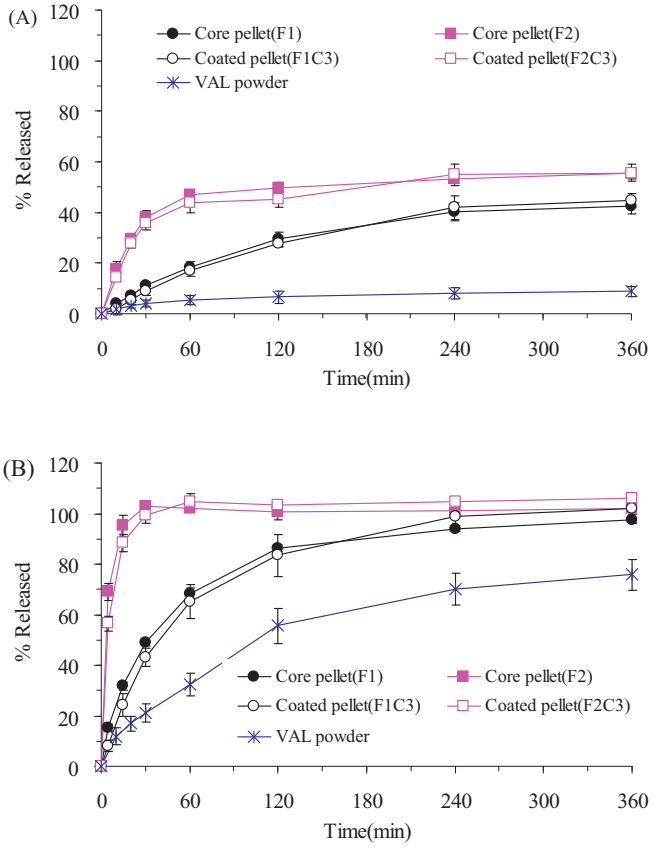

Fig. 5. Release profiles of VAL from core and coated pellets in simulated gastric (pH 1.2, A) and intestinal (pH 6.8, B) fluids. F1 and F2 were the core pellets without or with poloxamer 188 and NaOH in core composition, respectively. Composition of coating material (C3) was a mixture of HPMC and CB (1:2, w/w) and the coating level was 15%. Each data point represents the mean ± S.D. of three determinations.

poloxamer188 (Dumortier et al., 2006; Park et al., 2010) and NaOH (Ha et al., 2011; Tran et al., 2008, 2010a, 2011) incorporated in the core composition. In order to explain the enhanced drug release, the VAL crystallinity and the molecular interactions between VAL and the carriers were evaluated in details as follows.

We ever conducted XRDs and DSC scans of VAL, Avicel® PH 101, Povidone® K30, Poloxamer, NaOH and core pellet powders (F1 and F2). But the XRD analysis could not provide any information about the crystallinity of VAL due to low signal (data not shown). In addition, the DSC curve of pure VAL exhibited a broad single endothermic peak, while no melting drug peak was observed in the cases of both F1 and F2 pellets (data not shown). This phenomenon implied that there was some impact between VAL and additives during extrusion process.

Because the XRD diffractograms and DSC thermograms of F1 and F2 pellets powders did not fully illustrate the differences in drug dissolution rate, we investigated the molecular interactions between the drug and the carriers by FT-IR spectroscopy. The interaction between molecules can lead to changes in bonding between functional groups, which can be observed by FT-IR spectroscopy. Fig. 6 shows the FT-IR spectra of VAL, F1 and F2 core pellets. Pure VAL has two characteristic carbonyl absorption bands at 1734 and 1623 cm^{-1} that corresponded to carboxyl and amide carbonyl stretching, respectively (Tapas et al., 2010). These bands are of diagnostic value to elucidate drug–excipient interactions (Pravin et al., 2009). Therefore, we focused on these carbonyl groups to investigate the molecular interactions between the drug and the carriers.

The characteristic carboxyl carbonyl band in the F1 core pellets was shifted from 1734 to 1728 cm^{-1}, whereas no such band

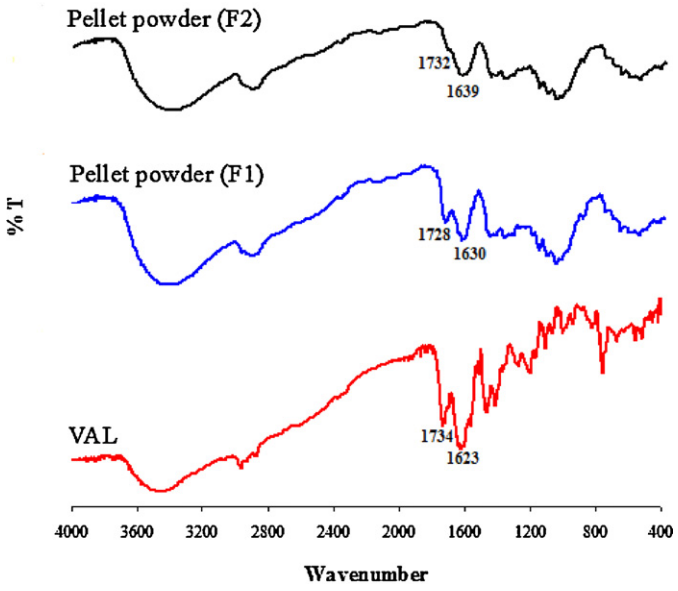

Fig. 6. FT-IR spectra of VAL and core pellet powders (F1 and F2).

was observed in the F2 core pellets. It could be attributed to strong hydrogen bonding between the drug and carriers indicating the drug carrier interaction (Pravin et al., 2009). On the other hand, the amide carbonyl stretching of the F1 and F2 core pellets were shifted from 1623 to 1630 cm^{-1}, 1623 to 1639 cm^{-1}, recording higher wave numbers than the drug alone. This shift of the absorption band of the amide carbonyl group can be attributed to breakdown of the intermolecular hydrogen bonds associated with the crystalline structure of drug and the formation of hydrogen bonding interactions (Pravin et al., 2009). Moreover, a lowered frequency of the carbonyl stretching from carboxylic acid was an indicator of those interactions (Cappello et al., 2006). Thus, the F2 core pellets exhibited the strongest molecular interactions between drug and carriers as seen from the large band shift in Fig. 6, which may correlated with the highest dissolution rate of VAL in release study. As aforementioned, the increased dissolution of VAL from core pellets were attributed to strong molecular interaction between drug and carriers, solubilizing effect of poloxamer 188, and pH modulation by NaOH.

Swelling of polymers is an important indication of their ability of mucoadhesion (Wang and Tang, 2008). To develop coated pellets with maximum adhesion strength, the ratio of HPMC to CB needs to be optimized for dry powder-coating. The swelling behavior of the coated pellets can be described by determining the water uptake capacity as described previously. Fig. 7 shows the effect of HPMC:CB ratio on the water uptake of coated pellets. As the ratio of HPMC to CB in the coating layer decreased, the water uptake property of the pellets increased for both F1 and F2 core. It was observed that, compared with core pellets, coated pellets had significantly higher water uptake, despite of the ratios of HPMC to CB at 15% of the coating level. Especially, the coated pellets (C3) with 1:2 of HPMC:CB coating showed higher water uptake when compared to the pellets (C1 and C2) coated with 2:1 or 1:1 of HPMC:CB ($p < 0.05$). However, no significant difference in water uptake was found between the core pellets, *i.e.* F1 and F2. It could also be seen between the corresponding coated pellets with different polymer ratios. Hence, it suggests that the core composition did not affect the water uptake, but the dissolution rate of the drug from the core pellets.

In fact, if the swelling level due to the water uptake is excessive, the bioadhesive power decreases because a large number of polymer binding sites are involved in bonds with water molecules, reducing thus the number of groups available to interact with

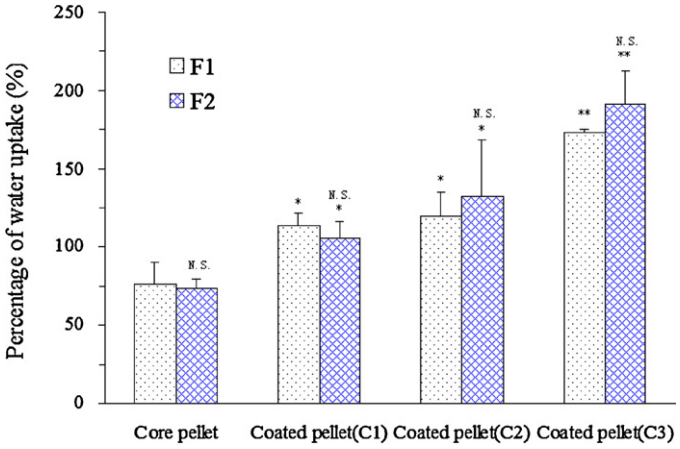

Fig. 7. Effect of HPMC:CB ratio on water uptake of coated pellets. F1 and F2 were the core pellets without or with poloxamer 188 and NaOH in core composition. The weight ratios of HPMC to CB in coating layer were 2:1, 1:1 and 1:2 for C1, C2 and C3, respectively. The coating level was 15%. Each value represents the mean ± S.D. of three determinations. $^{*}p < 0.05$, $^{**}p < 0.01$ compared with core pellet. $^{N.S.}$ difference is not significant compared with F1 group ($p > 0.05$).

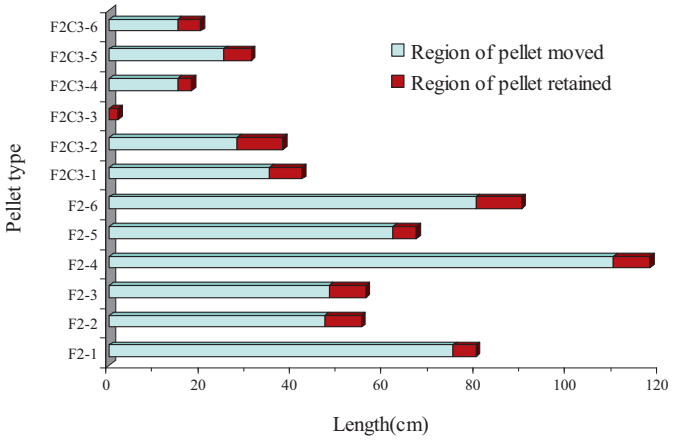

Fig. 9. Mucoadhesion properties of core (F2) and coated (F2C3) pellets in gastrointestinal tract at 6 h following oral administration in rats ($n = 6$). F2 was the core pellet incorporated with poloxamer 188 and NaOH in core composition. F2C3 was the coated pellet with a mixture of HPMC and CB (1:2, w/w) and the coating level was 15%. Each preparation was tested in six individuals.

mucin chains (Perioli et al., 2011). Although CB showed a higher capacity of water uptake than HPMC, it was blended with HPMC to achieve a suitable bio-adhesion function, because the mixture of HPMC and CB has shown a better swelling property than CB or HPMC alone (Llabot et al., 2002).

Several polymers and hydrophilic macromolecules containing groups that are able to form hydrogen bonds have showed good adhesion properties (Ikinci et al., 2004; Perioli et al., 2004, 2011). Fig. 8 shows the effect of HPMC:CB ratio in coating layer on the adhesion force of the coated pellets. The pellets (C3) coated with a lower ratio of HPMC:CB (1:2) exhibited the best *in vitro* mucoadhesion property and significant difference as compared to the C2 (1:1) and C1 (2:1) pellets for both F1 and F2 cores ($p < 0.01$). Likewise, it was observed by comparing Fig. 7 and Fig. 8 that the mixture of HPMC and CB that showed a higher adhesion force also presented a higher water uptake. It seems that a fast hydration of the polymer-coated layer with high water-uptake, led to an increased swelling of polymer layer, and thus affects the mucoadhesion property of coated pellets. However, the core pellets (F1 and F2) did not show any adhesion properties, although they exhibited about 75%

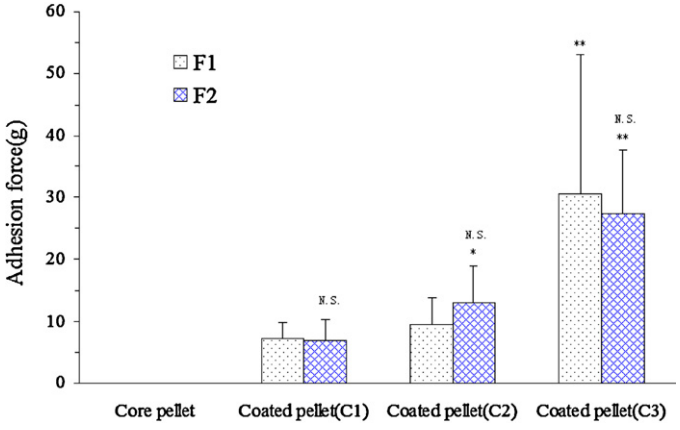

Fig. 8. Effect of HPMC:CB ratio on the adhesion force of coated pellets. F1 and F2 were the core pellets without or with poloxamer 188 and NaOH in core composition. The weight ratios of HPMC to CB in coating layer were 2:1, 1:1 and 1:2 for C1, C2 and C3, respectively. The coating level was 15%. Each value represents the mean ± S.D. of five determinations. $^{*}p < 0.05$, $^{**}p < 0.01$ compared with coated pellet (C1). $^{N.S.}$ difference is not significant compared with F1 group ($p > 0.05$).

of water uptake as shown in Fig. 7. This could be attributed to the absence of hydration and swelling properties of the core pellets.

The lack of *in vitro*/*in vivo* correlation among mucoadhesive fracture strengths reflected that polymers that produced strong mucoadhesive forces *in vitro* may not achieve prolonged gastrointestinal residence *in vivo* yielding increased bioavailability of a therapeutic agent (Laulicht et al., 2009). This was likely due to the different environment between the *in vitro* and *in vivo* conditions (Bernkop-Schnurch et al., 2004; Chary et al., 1999; Hagesaether et al., 2009). It is widely acknowledged that the extent of drug absorption in GI tract is related to the contact time of the drug with the small intestinal mucosa. In this study, the *in vivo* mucoadhesive properties of the formulations were compared in rat GI tract. The residence time and transit state of the core (F2) and coated pellets (F2C3) in GI tract at 6 h following oral administration in rats are shown in Fig. 9. It was clearly observed that the dry powder-coated pellets displayed shorter lengths of transit in GI tract compared with the core pellets. In each rat GI tract, the coated pellets showed less than 45 cm of transit length, and the pellets were retained in the upper region of the GI tract (mainly in small intestine) after 6 h of oral administration. In one of the rats, the pellets were still retained in the stomach. However, in all rats dosed with the core pellets, the pellets showed more than 50 cm of GI transit. Moreover, some core pellets were even observed in the caecum or colon of three of the rats. The results suggested that the dry powder-coating could render the core pellets considerable mucoadhesive effects *in vivo*, which is in good agreement with the adhesive forces observed in *in vitro* study (Fig. 8).

The pharmacokinetic parameters of VAL were determined after oral administration of the VAL suspension, core pellets (F2), and coated pellets (F2C3) in rats. The VAL-loaded core pellets (F2) was incorporated with poloxamer 188 and NaOH as solubilizer and pH modulator, and the coated pellets (F2C3) were layered with 1:2 of HPMC:CB at a coating level of 15%. Fig. 10 shows the mean plasma concentration–time curves of VAL after oral administration to rats at a dose of 1.44 mg (VAL)/kg. The mean plasma concentration of the drug from the coated pellets was remarkably higher than those from the core pellets and drug suspension. In particular, the coated pellets gave considerably higher plasma concentrations than the other preparations from 2 to 12 h. However, the higher initial plasma drug concentrations were observed in VAL suspension group. This might have been due to the high dispersibility and rapid absorption property of the drug powder at the upper site of GI tract (Tarur et al., 2008).

Table 4
Pharmacokinetic parameters of VAL following oral administration of VAL suspension, core (F2) and coated pellets (F2C3) in rats.

Pharmacokinetic parameters	VAL suspension	Core pellet (F2)	Coated pellet (F2C3)
C_{max} (μg/mL)	1.80 ± 0.93	2.10 ± 1.46$^{N.S.}$	3.60 ± 2.61$^{**,\#}$
T_{max} (h)	1.26 ± 1.30	5.08 ± 3.14**	3.50 ± 2.29$^{**,\#}$
AUC_{0-12} (μg h/mL)	6.80 ± 6.40	12.18 ± 7.89**	23.51 ± 17.69$^{**,\#\#}$

Each value is the mean ± S.D. of six separate determinations.
$^{N.S.}$ difference is not significant ($p > 0.05$).
** $p < 0.01$ compared with VAL suspension.
$^{\#}$ $p < 0.05$ compared with core pellet.
$^{\#\#}$ $p < 0.01$ compared with core pellet.

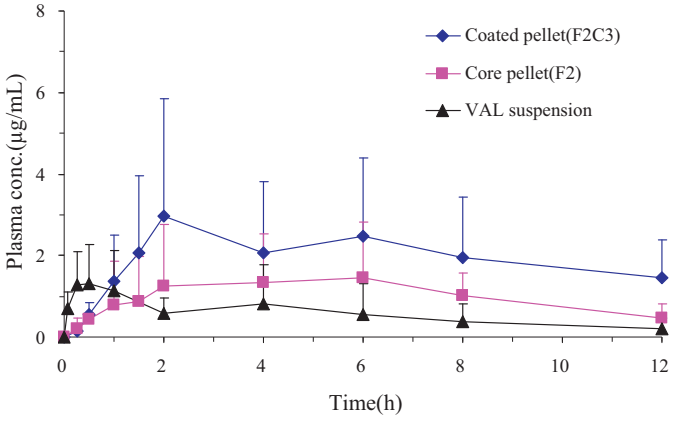

Fig. 10. Plasma concentration–time curves of VAL following oral administration of VAL suspension, core (F2) and coated (F2C3) pellets in rats, respectively. F2 was the core pellet incorporated with poloxamer 188 and NaOH in core composition. F2C3 was the coated pellet with a mixture of HPMC and CB (1:2, w/w) as coating material and the coating level was 15%. Each data point represents the mean ± S.D. of six separate determinations.

The pharmacokinetic parameters are shown in Table 4. The coated pellets gave a significantly higher AUC and C_{max} of the drug than VAL suspension ($p < 0.01$) or the core pellets ($p < 0.05$). In particular, the AUC of the coated pellets was about 1.9 and 3.5 fold higher than those from the core pellets and VAL suspension, respectively. The C_{max} of the coated pellets was about 1.7 and 1.8 fold higher than those of the core pellets and VAL suspension. On the other hand, the core pellets also showed a 1.8 fold higher AUC of the drug than VAL suspension ($p < 0.01$), while no significant difference of C_{max} was observed between these two preparations. However, the T_{max} of the core pellets or coated pellets were significantly lower than that of the drug suspension ($p < 0.01$), indicating the enhanced oral bioavailability of the dry powder-coated pellets is due to the marked increase in the mucoadhesive property in GI tract, and enhanced dissolution rate of the drug from the core pellets.

4. Conclusions

In this study, novel mucoadhesive polymer-coated pellets with enhanced bioavailability were successfully designed for VAL by using a dry powder-coating technique. The core pellets containing poloxamer 188 as a solubilizer and NaOH as a pH modulator showed significantly higher drug release rate than common pellets or drug powder *in vitro*. The coating of mucoadhesive polymers, *i.e.* HPMC and CB, did not alter the drug release pattern from the coated pellets, which showed almost identical release profiles as the core pellets. Strong molecular interactions between the drug and the carriers were demonstrated by FI-IR analysis. The powder-coated pellets coated with a mixture of HPMC and CB (1:2) showed desirable swelling performance and mucoadhesive property *in vitro*, as well as extended GI transit *in vivo*. In addition, this dry powder-coated pellets gave the significantly higher AUC and C_{max} compared to the core pellets (1.9 and 1.7 fold) or drug suspension (3.5 and 1.8 fold) in rats. Thus, our results suggest that the mucoadhesive pellets could render poorly water soluble drugs like VAL with a rapid drug release, extended GI transit and enhanced oral bioavailability.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2012.05.076.

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