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Preparation and in vitro/in vivo evaluation of sustained-release venlafaxine hydrochloride pellets

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ABSTRACT

The objective of this study was to prepare different venlafaxine hydrochloride sustained-release products and to elucidate the influence of composition of the coating film on the in vitro drug release profiles and in vivo pharmacokinetics. Pellets were prepared by a standardized process of extrusion/spheronization. A selected fraction size (0.8–1.0 mm diameter) of pellets of each formulation was coated with Eudragit® NE30D or ethylcellulose (10 cps). Many efforts have been made to tailor drug release rate by choosing different coating materials, different percent of pore forming components and coating weight variation to achieve a desired sustained-release effect. The dissolution studies were performed and data were analyzed in terms of cumulative release as a function of time. The influence on the release of venlafaxine from sustained-release capsules was observed in dissolution media of different pH and gradient pH. Scanning electron microscope (SEM) micrographs revealed morphological changes of the pellet coating surface which were related to in vitro drug release profiles. The relative bioavailability for Formulation 1 and Formulation 2 was evaluated in six healthy beagle dogs after oral administration in a fast state using sustained-release capsules (Effexor® XR) as a reference. The results suggested that Formulation 1 and Formulation 2 both had better bioavailability compared with Effexor® XR. It could be found that there existed quite difference in the in vivo release and oral absorption performances, despite the similar in vitro drug release behavior for the two formulations. It might be attributable to complex in vivo environment and then variation in the release behavior. Thus differences in the film micro-structure and surface roughness caused by aqueous dispersion and organic solvent coating techniques strongly influence the in vivo release and oral absorption performances.

1. Introduction

Venlafaxine is a bicyclic phenylethylamine derivative, which is a unique antidepressant structurally differs from other currently available antidepressants (Holliday and Benfield, 1995; Morton et al., 1995). The efficacy and tolerability profile of venlafaxine has been attributed to its inhibition of neuronal reuptake of serotonin and norepinephrine with a low affinity for muscarinic cholinergic, histaminergic or alphaadrenergic adrenergic receptors (Muth et al., 1986, 1991). The steady state half lives of venlafaxine and o-desmethylvenlafaxine (ODV, active metabolite of venlafaxine) are 5 and 11 h, respectively, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug (Troy et al., 1995). Venlafaxine extended-release (ER) capsules (Effexor® XR) were developed by Wyeth Pharmaceuticals to be taken once daily. The ER capsule contains spheroid particles, and release of drug was controlled by diffusion of these spheroids through the coating membrane.

We aimed to develop a sustained release dosage form of venlafaxine in the pellet form of capsules to be taken once daily. In comparison to single-unit dosage forms, sustained-release dosage forms based on pellets offer the advantage of allowing a more predictable gastric emptying, with an evacuation through the pylorus spread over a longer period of time and a gastric emptying which is less dependent on the nutritional state since the subunits are sufficiently small to be evacuated through the pylorus during the digestive phase (Follnier and Doelker, 1992). Film coating is a common process to modify drug release characteristics. When the drug-release behavior of film-coated pellets is well controlled, it can deliver predictable drug concentration within therapeutic range for a prolonged period of time, consequently improving the therapeutic effects of medical treatment.

The release rate from film-coating pellets could be finely tuned by the film thickness and composition (Haddish-Berhane et al., 2006). To date, the product design and development of new

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multiparticulate systems have been still largely carried out in an empirical manner (Ringqvist et al., 2003). For film-coating pellets, not only was coating polymer weight-gain a relatively non-specific measurement (Ho et al., 2008, 2009) but also the film coating thickness uniformity of a pellet was quite often related to undulations of the drug layer underneath (Heinicke and Schwartz, 2004).

In this work, many efforts have been made to modulate drug release rate by choosing different coating materials, different excipients as pore forming components and coating weight variation to achieve a desired sustained-release effect. The dissolution studies were performed and data were analyzed in terms of cumulative release as function of time. The influence on the in vitro release of venlafaxine from sustained-release capsules was observed in dissolution media of different pH and gradient pH. Scanning electron microscope (SEM) micrographs revealed morphological changes of the pellet surface that were related to an alteration in film coat composition.

In this work, we intended to develop two kinds of formulations of sustained-release capsules for the oral delivery of venlafaxine, to identify the factors influencing drug release performance, and to compare their physicochemical and pharmacokinetic characteristics with the commercial available product.

2. Materials and methods

2.1. Materials

Venlafaxine hydrochloride (VH) was purchased from North China Pharmaceutical Group Co., Ltd. (Hebei, China). Effexor® XR was purchased from Wyeth-Ayerst (Shenyang, China). Avicel® PH 101 (microcrystalline cellulose, MCC) was purchased from Asahi Kasei (Tokyo, Japan). Hydroxypropyl methyl cellulose (HPMC, 5 cps) was obtained from ZhanWang Pharmaceutical Co., Ltd. (Zhejiang, China). Tween80 was kindly provided by BASF (Wasserburg, Germany). Eudragit® NE30D was kindly provided by Degussa (Esson, Germany). Ethylcellulose (10 cps) was a gift from Colorcon (Philadelphia, USA). PEG6000 was purchased from Tianjin Bodi Chemical shares of chemical reagents (Tianjin, China). HPLC-grade methanol and acetonitrile were purchased from Fisher Scientific (Pittsburgh, PA, USA). Water was prepared using an EASYPURE®IIRF/UV ultrapure water system (Barnstead International Co., Boston, MA, USA). All other materials were of analytical grade and used as received.

2.2. Methods

2.2.1. Drug–excipient interaction studies

The possibility of drug–excipient interaction was investigated by differential scanning calorimetry (DSC). The DSC thermograms of pure drug, individual excipients and drug–excipient mixtures were recorded. The samples were separately sealed in aluminum cells and set in DSC-60 thermal analytical apparatus. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10 °C/min over a temperature range of 30–300 °C. Alumina was employed as the reference standard.

2.2.2. Preparation of drug-loaded cores

Venlafaxine hydrochloride loaded cores were prepared via extrusion–spheronization technique. The compositions of drug-loaded pellets are given in Table 1. A uniform powder mixture of drug and excipients was wet massed by the addition of a liquid binder. Then obtained wet mass was extruded at 30 rpm in an axial screen extruder (WL 350, Wenzhou, China) equipped with an axial screen with dies of 1 mm diameter and 1 mm length. The extrudate was spheronized in 100 g quantities for 5 min at 1800 rpm on a 250 mm radial plate spheronizer (WL 350, Wenzhou, China) using a cross-hatch frictional plate of 3 mm × 3 mm pitch and 1.2 mm depth. The produced drug-loaded cores were then dried for 12 h at 40 °C in a drying oven.

Table 1
Composition of the venlafaxine hydrochloride loaded cores.

Ingredients	% (w/w)
VH	42.5
MCC	45.5
SiO_2	2

2.2.3. Sustained-release pellets

2.2.3.1. Preparation of Formulation 1. Drug-loaded cores were coated with Eudragit® NE30D containing small amounts of PEG6000 in a fluidized bed coater. The coating dispersion was prepared as follows: Eudragit® NE30D was diluted to a solid content of 10% (w/w). After aqueous PEG6000 was added, the blends were stirred for 30 min prior to coating. The process parameters were as follows: inlet temperature = 20 °C, product temperature = 20 ± 2 °C, spray rate = 1 mL/min, atomization pressure = 0.2 Mpa, blast pressure = 0.3 Mpa, the pellets were further fluidized for 10 min and subsequently cured for 24 h at 60 °C. All the drug-loading cores were coated in a fluid bed coater using bottom spray until a weight-gain of 12% was achieved.

2.2.3.2. Preparation of Formulation 2. For the coating process, pellets were coated with blends of ethylcellulose and small amounts of PEG6000 in a fluid bed coater using bottom spray and Wurster insert until a weight-gain of 9% (w/w, based on the core pellet) was reached. The coating dispersion was prepared as follows: ethylcellulose was dissolved in 95% ethanol and plasticized over night with dibutyl sebacate. Aqueous PEG6000 was added, and the blends were stirred for 30 min prior to coating. The process parameters were as follows: inlet temperature = 50 °C, product temperature = 50 ± 2 °C, spray rate = 1 mL/min, atomization pressure = 0.2 Mpa, blast pressure = 0.3 Mpa, the pellets were further fluidized for 10 min and subsequently cured for 24 h at 40 °C. The film coating consisting of ethylcellulose and plasticizer amounts to about 12% of the weight of the diffusion pellets. The coating level was calculated by weight of the sprayed dispersion without the amount of HPMC.

2.2.4. Drug release measurements and comparisons

The release measurement was carried out at 37 °C in 900 mL of 6 kinds of dissolution media, using a dissolution apparatus (ZRS-8G Test Dissolution Tester, China). The test was performed with a basket rotation speed of 100 rpm which is specified in the Chinese Pharmacopoeia. The dissolution media used were water, pH 6.8 phosphate buffer, pH 7.2 phosphate buffer, 0.1 M HCl, pH 4.5 NaAc–HAc buffer solution and pH gradient medium. The prepared sustained-release capsules (Formulation 1, Formulation 2) and marketed Effexor® XR weighed to be equivalent to 75 mg of drug were added to the dissolution apparatus, respectively, and 1 mL of test fluid was withdrawn after 1, 2, 4, 8, 12 and 24 h. The withdrawn samples subsequently were filtered through a 0.45 μm millipore filter and assayed for the dissolved drug concentration by HPLC.

To reflect gastrointestinal environment in vivo, the pH gradient medium was used. The pH gradient medium was 0.1 M HCl during the first 2 h, then high concentration phosphate buffer was added to change the pH to 6.8, then high concentration phosphate buffer was added to change the pH to 7.2 at 4 h.

The HPLC system consisted of an L-7110 pump, a Jasco UV–vis detector L-1575 set at 226 nm and an ANASTAR interface (Tianjin, China). UV signals were monitored and peaks integrated using

Table 2
Model of drug release.

Model name	Equation
Zero-order model	$Q_t = k_0 t$
First-order model	$\ln(Q_0 - Q_t) = -k_1 t + \ln Q_0$
Higuchi diffusion model	$Q_t = k_H t^{1/2}$
Ritger–Peppas model	$\ln Q_t = n \ln t + k$
Hixson–Crowell model	$(1 - Q_t)^{1/3} = 1 - kt$
Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = kt$

ANASTAR HSM software. A calibration was previously performed and it was confirmed that excipients produced no absorption signal at this wavelength across a wide range of concentrations. Also, there was no interference in UV absorption between venlafaxine hydrochloride and these excipients, capsule shell. Chromatographic separations were performed at room temperature using a C_{18} column (Diamonsil®, 4.6 mm × 150 mm, 5 μm; Dikma Technologies) and a flow rate of 1.0 mL/min. The mobile phase consisted of acetonitrile: 0.01 M triethylamine–phosphate buffer solution (pH 3.0) (28:72, v/v) and was filtered through a 0.45 μm membrane filter and degassed by ultrasonication before use. These conditions resulted in a typical elution time for venlafaxine hydrochloride of 5.5 min.

To compare the dissolution profiles of test preparations and marketed sustained-release capsules in various media simulating different physiology pH, dissolution was performed in water, pH 6.8 phosphate buffer solution, pH 7.2 phosphate buffer solution, 0.1 M HCl, pH 4.5 NaAc–HAc buffer solution and pH gradient medium. Similarity index was introduced by Moore and Flanner in 1996 to determine similarity of two profiles and is defined as follows (Moore and Flanner, 1996):

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where n is the sample number, and R_t and T_t are the percentages of the reference and test drug release, respectively, at different time intervals t. The f_2 value is between 0 and 100. The value is 100 when the test and the reference profiles are identical and approach zero as the dissimilarity increases, but because f_2 is a log function small differences in profile lead to a large drop in f_2. If f_2 of two dissolution drug release profiles is between 50 and 100, then these two drug release profiles are similar. Value under 50 indicates differences between the release profiles (Costa and Lobo, 2001).

2.2.5. Scanning electron microscopy and electron microscope imaging

To examine the morphology of the drug and film coating layer, scanning electron microscopy (SEM, ZEISS, Carl Zeiss Jena) images were obtained for pellets from Formulation 1, Formulation 2 and marketed Effexor® XR after dissolution. For analyzing the drug release mechanisms, the electron microscope (Motic, DMBA450, China) pictures were taken at magnification of 40×.

2.2.6. Drug release mechanism

Drug release data were analyzed by various mathematical models. Seven kinetic models including zero order, first order (Dredan and Istvan, 1996), Higuchi (Higuchi, 1963), Ritger–Peppas (Ritger and Peppas, 1987), Hixson–Crowel (Baker and Lonsdale, 1974) and Baker–Lonsdale release equations were applied to process the in vitro release data. The equations are shown in Table 2.

In Table 2 Q_t is the drug released fraction at time t, k_0 is the zero order release rate constant, k_1 is the first order release rate constant and k_H is the Higuchi's release rate constant, t is the release time, n is the parameter that depends on the release mechanism and the shape of the matrix tested. The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods. Regression analysis was performed and best fits were calculated on the basis of correlation factors as r^2.

For further analyzing the drug release mechanism, the Harland (Koichiro et al., 1995; Peppas and Sahlin, 1989) equation was used.

$$Q_t = \alpha t^{1/2} + \beta t$$

where Q_t is the drug released fraction at time t, α is the Fickian diffusional rate constant and β is the relaxational rate constant, and the percent of Fickian diffusion (1) or relaxation (2) was calculated by following equations:

$$F = \frac{1}{1 + \beta/\alpha \times t^{1/2}} \quad (1)$$

$$R = \frac{1}{\alpha/\beta \times t^{-1/2} + 1} \quad (2)$$

2.2.7. In vivo studies

2.2.7.1. Experimental design. This was an open label, randomized, three-period crossover study in dogs. The experiments for the evaluation of the pharmacokinetic study in dogs were approved by the Ethics Committee for Animal Experimentation of Shenyang Pharmaceutical University (Shenyang, China).

A total of six healthy male beagle dogs, fasted but free access to water for 12 h prior to the experiment, were used in the study. And the dogs (7–10 kg) were kept in these facilities for at least 1 week prior to these experiments. The experiment involves fasting, single dose with the three different preparations with wash out period in between. The preparations (Formulation 1, Formulation 2 and reference product) containing 75 mg of drug were administered in the morning and standard lunch was given 4 h after dosing.

Blood was withdrawn via cannulated needle from front legs.

Blood samples (3.0 mL) were collected in heparinized tubes immediately prior to dosing (time zero) and at 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 30.0 and 36.0 h after dosing. The plasma was obtained by the centrifugation of blood at 3000 rpm for 10 min and then kept frozen at −20 °C until analysis. The concentrations of venlafaxine in plasma were determined by ultra performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS).

2.2.7.2. Determination of venlafaxine in dog plasma. A selective, rapid and sensitive UPLC–MS/MS method was developed for the quantification of venlafaxine in dog plasma. With glipizide as an internal standard, sample pretreatment utilized a simple precipitating protein. A methanol solution of internal standard (40 μg/mL) 50 μL and 50 μL mobile phase were added to 50 μL plasma. After vortex-mixing for 1 min, the samples were centrifuged at 15,000 rpm for 10 min. And the supernatant was collected and centrifuged under the same conditions. The separation was carried out on an ACQUITY UPLCTM BEH C18 column (50 mm × 2.1 mm, 1.7 μm; Waters Co., Milford, MA, USA) with water (containing 0.1% formic acid) and acetonitrile as the mobile phase at the flow rate of 0.2 mL/min. The detection was performed by a Waters Tandem Quadrupole (TQ) Detector (Waters, USA). The mass spectrometer was operated with electrospray ionization (ESI) interface in positive ionization mode and with multiple-reaction monitoring mode. The selected reaction monitoring (SRM) of venlafaxine and the internal standard were m/z 278.1 → 58 (venlafaxine), m/z 446.3 → 312.2 (glipizide), respectively. The concentration of venlafaxine was determined by a standard linear calibration curve in the concentration range of 2–5000 ng/mL.

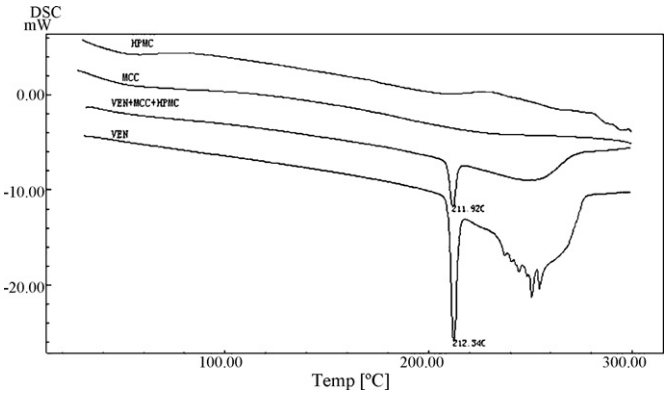

Fig. 1. Differential scanning calorimetry curves for blank excipients, drug and physical mixture.

2.2.7.3. Pharmacokinetic data analysis. Non-compartmental pharmacokinetic analysis was conducted to calculate the area under the curve from 0 to 36 h (AUC_{0-36}). The peak plasma concentration (C_{max}) and the time to reach peak plasma concentration (T_{max}) of the different dosage forms were determined by a visual inspection of the experimental data. The AUC was estimated according to the linear trapezoidal rule. The threshold for differences to be considered significant was set at $p \leq 0.05$. The relative bioavailability of Formulation 1 and Formulation 2 to the commercial capsules (reference) was calculated using the following equation:

$$\text{Relative bioavailability}\,(\%) = \frac{AUC_{0-36}\text{test}}{AUC_{0-36}\text{reference}} \times 100$$

Additionally the ratios and 90% CIs of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were calculated for three formulations, and 2 one-sided *t* tests were used to evaluate whether the 90% CIs of the geometric mean ratios (test:reference) for these parameters were within the range of 80.00–125.00 (using log transformed data).

2.2.8. In vitro–in vivo correlations (IVIVC) analysis

An IVIVC for venlafaxine was evaluated by plotting the percent dissolved (*F*) of the three formulations versus the percent absorbed (F_a) in vivo. Percent dissolved values were taken from in vitro release data in different media, and percent absorbed was determined by the Wagner–Nelson method using the following equation:

$$F_a\,(\%) = \frac{C_p + k_e AUC_{0-t}}{k_e AUC_{0-\infty}} \times 100$$

where F_a is the fraction of drug absorbed, C_p is the drug plasma concentration at time *t*, k_e is the elimination rate constant, AUC_{0-t}, and $AUC_{0-\infty}$ are areas under the curve between time zero and time *t* and between time zero and infinity, respectively. Linear regression analysis was applied to fit the data and *R* was calculated to evaluate the robustness of IVIVC.

3. Results and discussion

3.1. Drug–excipient interaction by differential scanning calorimetry (DSC)

DSC curves obtained for venlafaxine, MCC, HPMC and the physical mixtures are shown in Fig. 1. The DSC thermogram for venlafaxine showed a sharp melting endothermic peak at 212.3 °C. The individual excipients did not show any characteristic peaks. There was no shift in the endotherm peak of venlafaxine in the drug–excipient physical mixtures, indicating good biocompatibility of the drug with all the excipients.

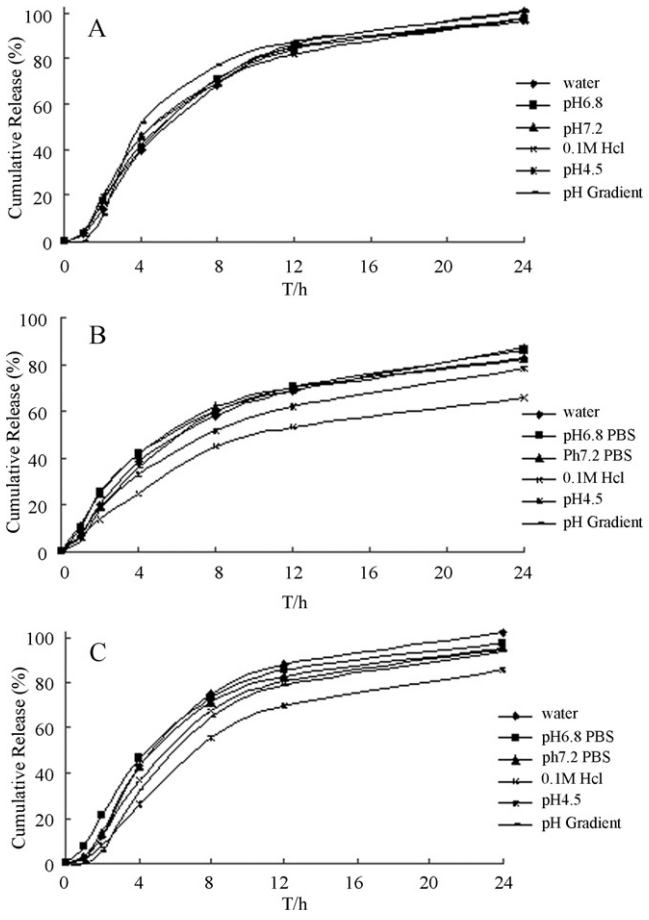

Fig. 2. Release curves of VH from sustained-release pellets: (A) Formulation 1, (B) Formulation 2, and (C) Effexor® XR.

3.2. In vitro dissolution testing

The in vitro dissolution profiles of Formulation 1, Formulation 2 and Effexor® XR (reference) are shown in Fig. 2. Formulation 1 coated with Eudragit® NE30D exhibited similar drug release behavior in different dissolution media, while Formulation 2 and Effexor® XR exhibited slower release in 0.1 M HCl and pH 4.5 NaAc–HAc buffer solution than in other high pH media. The results showed that drug release rate of Formulation 2 and Effexor® XR in the first 4 h was much slower than that of Formulation 1. The decreased drug release performance might be related to the coating technique. The pellets coated by ethylcellulose organic solution (Formulation 2 and Effexor® XR) showed extended release rate and lowered extent in lower pH media, especially in pH 4.5 NaAc–HAc buffer solution. There are nearly no differences in release behavior between various dissolution media for Formulation 1, this may be because that the characteristic of Eudragit® NE30D is neutral and non-sensitive to pH.

The similarity factors (f_2) which were calculated between the reference and Formulation 1/Formulation 2 are presented in Table 3. The results of f_2 showed that the profiles of Formulation 1 were mostly similar to the reference except in pH 4.5 NaAc–HAc buffer solution where the dissolution rate and extent of Formulation 1 were both superior to the reference. Based on the in vitro dissolution performances, it was expected that Formulation 1/Formulation 2 and reference products may be bioequivalent, but still needed further bioequivalence verification.

Table 3
Fit factors to compare the reference and test formulations in different mediums.

Mediums	f_2	
	F1	F2
Water	76.36	53.64
pH 6.8 PBS	73.92	57.93
pH 7.2 PBS	76.67	58.57
0.1 M HCl	73.45	68.38
pH 4.5 NaAc–HAc	45.16	61.83

3.3. SEM experiments

SEM images of dry pellets after dissolution for 24 h are shown in Fig. 3. Pellets coated with Eudragit® NE30D exhibited a relatively rough surface with small cracks and many pores distributed over the coating film. In contrast, Formulation 2 after 24 h exposure to the dissolution medium, showed a smoother appearance with some pores. Effexor® XR after 24 h dissolution had an even and non-porous surface. This might be due to the different film formation structures for the two coating techniques. As for organic solvent-based systems, the polymer solutions undergo sol to gel transitions upon solvent evaporation to finally form the polymeric films. However, when spraying aqueous polymer dispersions, the polymer particles are deposited on the surfaces of the solid dosage forms. The colloidal particles come into direct contact with each other and form close-packed arrays due to water evaporation and the interfacial tension between water and polymer. Capillary forces then drive the particles to coalesce together (Siepmann et al., 2008). As the interpenetration degree of polymer chain in aqueous dispersions is much lower than that in organic solution, films prepared from aqueous dispersions were mechanically much weaker and could more easily cause crack formation due to hydrostatic pressures generated within the pellets' core during drug release. This led to higher water permeability and swellability of membrane formed by Eudragit® NE30D (Formulation 1) than ethylcellulose organic solution film (Formulation 2 and Effexor® XR).

3.4. Drug release mechanism studies

The patterns of drug released from film-coating formulations were summarized as follows. (1) The membrane will start to absorb water and swell after contact with aqueous medium. Then fast water penetrates through the coats with membrane controlled drug delivery (Strübing et al., 2007a). Water permeates through the polymer film and dissolves the drug inside the pellet core. Swelling of coating polymers will continue until an equilibrium state is reached between the achievement of hydration that will promote the diffusion and the elastic strength of the polymer on the opposite. (2) A linear polymer or a sufficient hydrophilicity of the polymer will be solvated by the water in the dissolution medium (Ueberreiter and Asmussen, 1961; Ju et al., 1995). The leaching of pore-forming agents from the polymer coat into the dissolution medium creates pores which control the release of drug molecules. Due to an osmotic pressure difference water permeation into the pellets will continue until the core is water saturated and the transport processes through the membrane become diffusion controlled in both directions. The water influx induced swelling of the pellets is leading to an expansion of the polymer network and by this to a further increased permeability of the film coat (Strübing et al., 2007b). EMS pictures of three formulations (Fig. 4) exhibited insoluble membrane after dissolution for 24 h, which could improve that drug-release was partly controlled by film coat. And pores in membrane showed by SEM images (Fig. 3) indicated that some drug might release through pores.

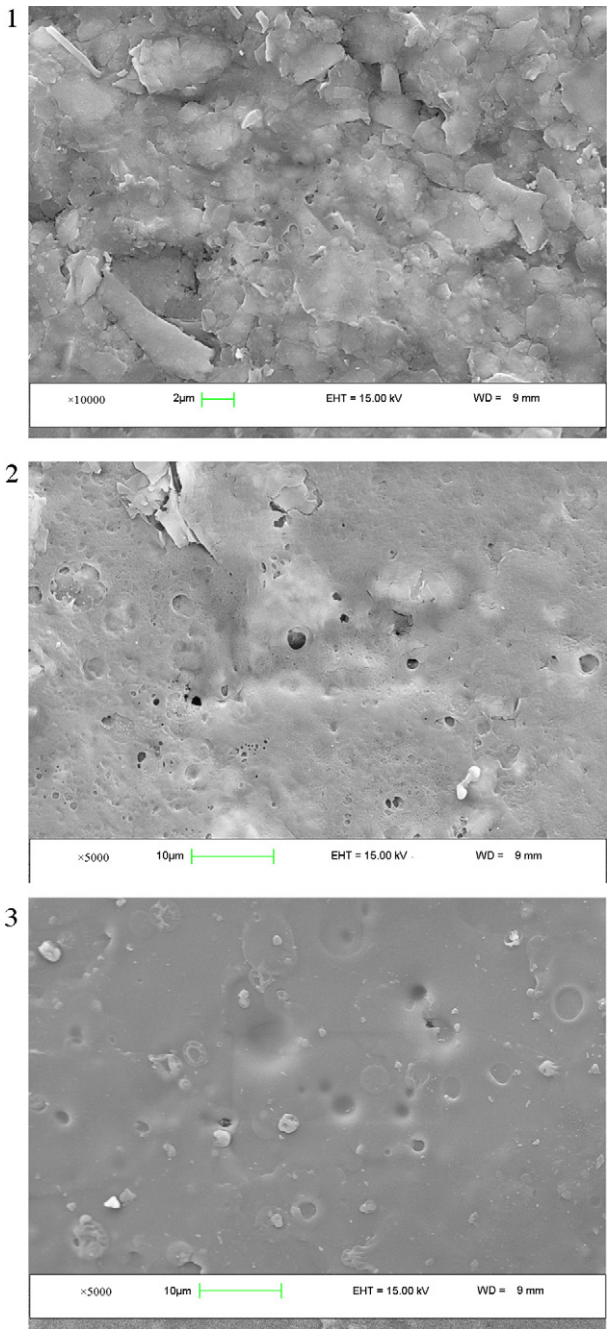

Fig. 3. (1) SEM graph of Formulation 1 after 24 h contact with water. (2) SEM graph of Formulation 2 after 24 h contact with water. (3) SEM graph of Effexor® XR after 24 h contact with water.

As shown in Table 4, through various types of regression model parameters and comparing, first-order model was chosen for it had the best regression fitting degree. And the data of Formulation 1, Formulation 2 and Effexor® XR showed values of "*n*" in Ritger–Peppas model between 0.45 and 0.89, which could be attributed to non-Fick Diffusion (Fig. 5).

3.5. Bioavailability studies

Bioavailability studies of the two optimal prepared sustained-release pellets of venlafaxine compared with commercial available capsules (Effexor® XR) were investigated following oral administration of 75 mg drug to six healthy beagle dogs. The profiles of the mean plasma concentrations of venlafaxine versus time are shown

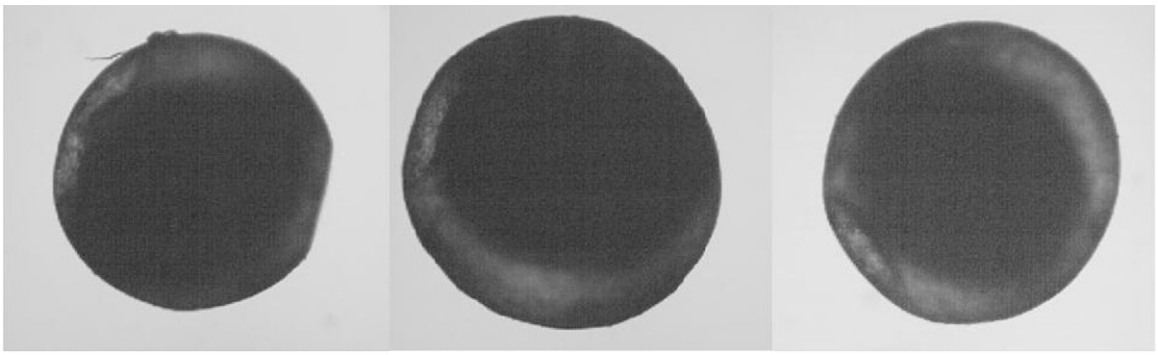

Fig. 4. Electron microscope graph of VH sustained-release pellets after 24 h contact with water: (A) Formulation 1, (B) Formulation 2, and (C) Effexor® XR.

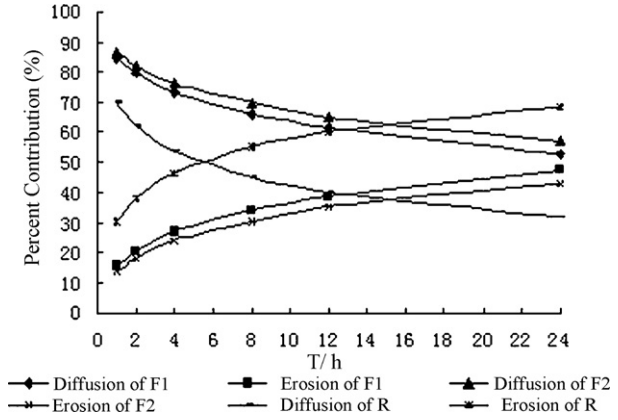

Fig. 5. The percentage contribution of the Fickian diffusion and the erosion mechanism of Formulation 1, Formulation 2 and Effexor® XR.

in Fig. 6 and the main pharmacokinetic parameters are shown in Table 5, respectively. After administration of Formulation 1, Formulation 2 and Effexor® XR, the drug was observed to achieve plasma levels rapidly. After 1 h, mean plasma concentrations of Formulation 1, Formulation 2 and Effexor® XR were 84.29, 159.88 and 106.33 ng/mL. The mean peak plasma concentrations for Formulation 1, Formulation 2 and Effexor® XR were 1922.19, 1090.24 and 1126.19 ng/mL and these were achieved at 6.5, 11 and 11 h, respectively. The relative bioavailability of venlafaxine from Formulation 1 compared with the reference calculated from AUC_{0-36} was 119.6%, and that of Formulation 2 compared with the reference was 101.1%. There were significant differences between Formulation 1 and Effexor® XR in T_{max}. This might attribute to the significant inter-individual variability of drug plasma concentration and less number of dog subjects. Then further study was required with more subjects to achieve more compelling results.

Table 4
Model simulated for the release profiles of VH sustained-release pellets.

Batch no.	Model	Equation	r
Formulation 1	Zero-order model	$Q_t = 0.0430t + 0.125$	0.9294
	First-order model	$\ln(Q_0 - Q_t) - \ln Q_0 = -0.1776t + 0.1729$	0.9972
	Higuchi diffusion model	$Q_t = 0.2356t^{1/2} - 0.0868$	0.9687
	Ritger–Peppas model	$\ln Q_t = 0.7448 \ln t + 2.4587$	0.9620
	Hixson–Crowell model	$(1 - Q_t)^{1/3} = 0.1514t + 4.5919$	0.9908
	Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = 0.0186t - 0.0224$	0.9948
Formulation 2	Zero-order model	$Q_t = 0.0356t + 0.1576$	0.9109
	First-order model	$\ln(Q_0 - Q_t) - \ln Q_0 = -0.0868t - 0.0781$	0.9986
	Higuchi diffusion model	$Q_t = 0.1983t^{1/2} - 0.03663$	0.9821
	Ritger–Peppas model	$\ln Q_t = 0.7937 \ln t - 2.3243$	0.9548
	Hixson–Crowell model	$(1 - Q_t)^{1/3} = -0.0965t + 4.447$	0.9746
	Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = 0.0108t - 0.009$	0.9933
Effexor® XR	Zero-order model	$Q_t = 0.0499t + 0.1321$	0.8978
	First-order model	$\ln(Q_0 - Q_t) - \ln Q_0 = -0.1752t + 0.0999$	0.9983
	Higuchi diffusion model	$Q_t = 0.2480t^{1/2} - 0.0936$	0.9585
	Ritger–Peppas model	$\ln Q_t = 0.8340 \ln t + 2.2946$	0.9750
	Hixson–Crowell model	$(1 - Q_t)^{1/3} = -0.0327t + 0.9767$	0.975
	Baker–Lonsdale model	$3/2[1 - (1 - Q_t)^{2/3}] - Q_t = -0.0174t - 0.0084$	0.9814

Table 5
Relative bioavailability and pharmacokinetic parameters of Formulation 1, Formulation 2 and Effexor® XR administered orally to the beagle dogs ($n = 6$).

Parameters	Effexor® XR	Formulation 1	Formulation 2
T_{max} (h)	11.67 ± 3.88	6.50 ± 2.07	11.67 ± 3.67
C_{max} (ng/mL)	1126.2 ± 563.8	1922.2 ± 1056.7	1090.2 ± 523.5
AUC_{0-t} (ng h/mL)	24141.0 ± 13488.9	25995.9 ± 12365.0	20730.4 ± 9473.4
$AUC_{0-\infty}$ (ng h/mL)	30304.1 ± 14602.7	29723.1 ± 16035.7	24152.7 ± 11636.4
Relative bioavailability (%)	–	119.6	101.1

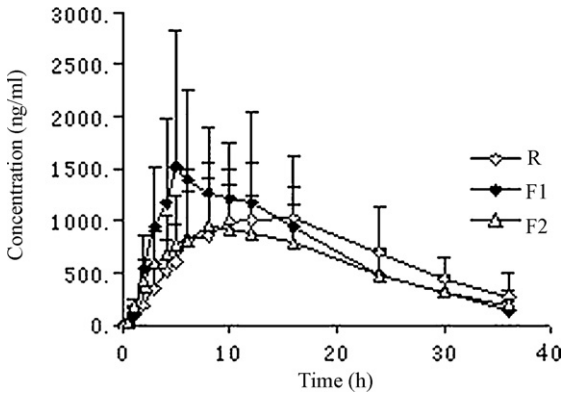

Fig. 6. Mean concentration–time curve after oral administration of the reference and the test venlafaxine hydrochloride capsules.

3.6. IVIVC

The level A of IVIVC in which the entire in vivo time course is correlated with in vitro data, was developed in this study. All the data of dissolution in 6 kinds of media and in vivo absorption were used. The regression analysis results are summarized in Tables 6–8, and non-linear relationships of F versus F_a for three formulations are shown in Fig. 7. The data demonstrated that the dissolution performance of the three venlafaxine formulations in 6 kinds of media all have good correlation between absorption in vivo and drug release in vitro. Though there were nearly no change in IVIVC of Formulation 1 in different release media, the significant difference between different dissolution media for IVIVC of Formulation 2 and Effexor® XR was observed. The results indicated that the dissolution in vitro of Formulation 1, Formulation 2 and Effexor® XR correlates best with in vivo absorption in water, 0.1 M HCl and 0.1 M HCl, respectively.

Table 6
Linear function of F and F_a in different media of Formulation 1.

Media	Function	r
Water	$F_a = 0.6080F - 4.3817$	0.9638
PBS of pH 6.8	$F_a = 0.6202F - 4.9718$	0.9545
PBS of pH 7.2	$F_a = 0.6251F - 5.7251$	0.9487
0.1 M HCl	$F_a = 0.6316F - 5.3561$	0.9554
pH 4.5 NaAc–HAc	$F_a = 0.6252F - 5.8437$	0.9439
pH gradient	$F_a = 0.5623F - 3.4610$	0.9326

Table 7
Linear function of F and F_a in different media of Formulation 2.

Media	Function	r
Water	$F_a = 0.8451F - 2.7102$	0.9923
PBS of pH 6.8	$F_a = 0.8665F - 5.2820$	0.9865
PBS of pH 7.2	$F_a = 0.8815F - 5.8195$	0.9833
0.1 M HCl	$F_a = 1.1189F - 2.5164$	0.9976
pH 4.5 NaAc–HAc	$F_a = 0.9508F - 3.0277$	0.9945
pH gradient	$F_a = 0.8651F - 1.9648$	0.9917

Table 8
Linear function of F and F_a in different media of Effexor® XR.

Media	Function	r
Water	$F_a = 0.9878F + 1.4579$	0.9964
PBS of pH 6.8	$F_a = 1.0708F - 3.8347$	0.9942
PBS of pH 7.2	$F_a = 1.0566F + 0.2925$	0.9948
0.1 M HCl	$F_a = 1.0773F + 1.4833$	0.9976
pH 4.5 NaAc–HAc	$F_a = 1.2010F + 4.3281$	0.9959
pH gradient	$F_a = 1.0596F + 5.3949$	0.9965

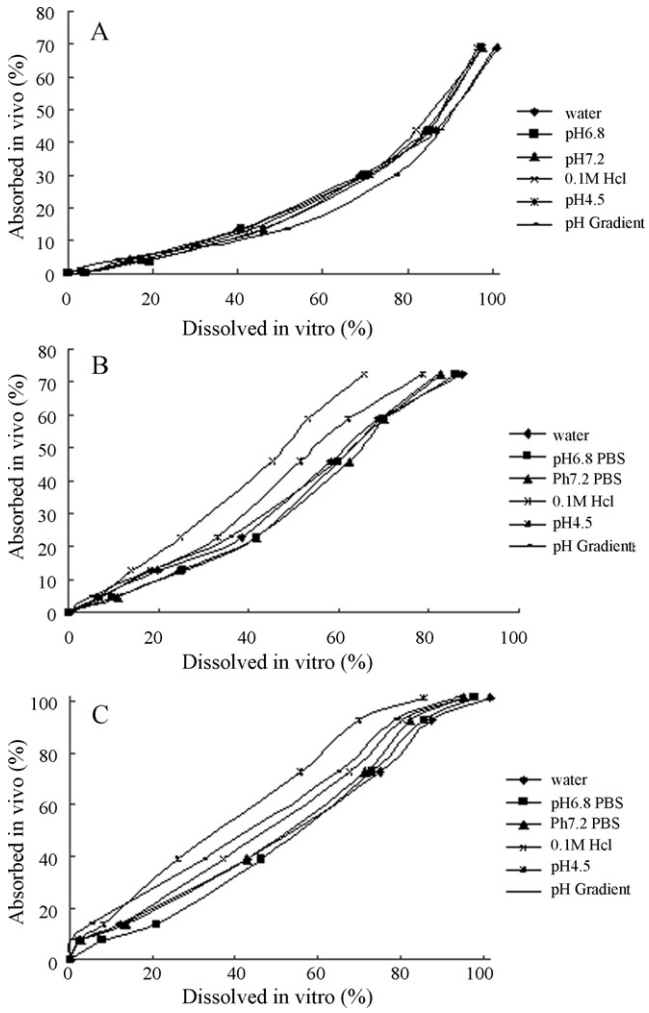

Fig. 7. Plot of VH absorbed in vivo versus drug dissolved in vitro for (A) Formulation 1, (B) Formulation 2, and (C) Effexor® XR.

Though formulations coated with different techniques could achieve similar drug release behavior in vitro by optimization of formulation and process parameters, in vivo oral absorption of Formulation 1 coated by solid dispersion was quite different from Formulations 2 by organic solution. This might be due to significant differences in the film micro-structure, and between in vitro and in vivo environment. Films formed by aqueous suspension had weaker mechanical feature, less dense polymer structures and rough surfaces, and then the macromolecular mobility and permeability increase. Though we investigated drug-release behavior in six kinds of media, the in vivo drug release process was strongly affected by gastrointestinal surfactants, transit and contraction, water content and fluid viscosity and so on, which could not be reflected truly by in vitro conditions. It could be concluded that differences in the film micro-structure and surface roughness by aqueous dispersion and organic solvent coating techniques strongly influence the in vivo absorption performances, despite similar in vitro release behavior.

4. Conclusion

To identify effects of different film-forming methods on in vitro release and in vivo pharmacokinetic performances, two different coating techniques, including aqueous dispersion and organic solvent coatings, were undertaken in this study. Release of both formulations was found to follow first-order kinetics and had

good correlation with in vivo absorption performance. It should be pointed out that variations in the film micro-structure and surface roughness can be of major importance for drug release behavior and in vivo pharmacokinetic performance. Films formed by organic solvent coating technique had better plasticity, higher density and more uniform surface than those by aqueous dispersion. Through optimizing formulation and preparative method, we successfully prepared two formulations coated with Eudragit® NE30D or ethylcellulose organic solution with similar in vitro release behavior, respectively. However, their in vivo absorption performances were significant different, because complex in vivo environment was difficult to be reflected truly by in vitro release conditions and then result in variation in the in vivo release behavior.

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