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Sustained-Release Pellets Prepared by Combination of Wax Matrices and Double-Layer Coatings for Extremely Water-Soluble Drugs

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This study was performed in order to develop a sustained-release pellet formulation containing venlafaxine hydrochloride (VEN), an extremely water-soluble drug, prepared by combination of wax matrices and double-layer coatings. The influence of both double-layer polymeric coats and wax matrices on the release of VEN from sustained-release pellets was investigated. The pellets were prepared by wet mass extrusion spheronization methods and then coated with a fluidized bed coater. For the pellets coated with Eudragit® NE30D alone, a coating level of nearly 40% was required to pass the dissolution test compared with commercial product, and it was accompanied by an unacceptable lag time. The application of an alcohol-soluble polymeric subcoat, Opadry® I, was added before the Eudragit® NE30D coating process, which resulted in a marked delay in drug release. However, a faster release was observed for the formulation coated with a high subcoat level (10%) at the end of the dissolution test. A further delay in drug release was observed when a wax matrix, octadecanol, was added to the core pellet formulation. The kinetics of drug release changed from the Higuchi model to a zero order model and the predominant mechanism controlling drug release changed from diffusion to dissolution upon increasing the amount of octadecanol within the matrix pellets. In addition, the drug release was markedly influenced by the drug to matrix ratio. In conclusion, the 40% drug-loaded core pellets with double-layer coatings (8% Opadry® I and 12% Eudragit® NE30D) and 20% octadecanol matrix produced the desired profile for once-daily sustained release compared with the commercial product, and these pellets remained stable during storage.

Keywords subcoat; Eudragit® NE30D; Opadry® I; wax matrix; sustained-release pellet

INTRODUCTION

It is generally agreed upon that multiple unit controlled-release dosage forms such as pellets offer some biopharmaceutical advantages, particularly regarding the duration and the individual reproducibility of gastric emptying, in comparison with larger single-unit dosage forms (Hamdani, Moës, & Amighi, 2002). Coating pellets with a polymer is commonly used for controlling the drug release rate from extended-release formulations (Heng, Hao, Chan, & Chew, 2004). A considerable amount of work has been devoted to the description of drug release from coated pellets (Göran, Åsa, & Göran, 2003; Ozturk, Ozturk, Palsson, Wheatley, & Dressman, 1990). Several authors have reported that due to the migration of the water-soluble drug into the aqueous film during the coating process, highly water-soluble drugs require higher polymer coating levels than poorly soluble compounds for sustained or delayed drug release, which results in a longer lag time for initial release (Diane, Koleng, & McGinity, 2003; Ghebre-sellassie, Gordon, Nesbitt, & Fawzi, 1987; Li, Feld, & Kowarski, 1997; Rekhi, Porter, & Jambhekar, 1995). An organic polymer coating solution can be used to avoid this problem by lowering drug solubility in organic coating solvents (Umprayn, Chitropas, & Amarekajorn, 1999). The current commercial product of venlafaxine hydrochloride (Effexor® XR), a unique antidepressant equivalent to venlafaxine 75 mg in the form of extended-release pellets, consists of venlafaxine hydrochloride, microcrystalline cellulose (MCC), and, optionally, hydroxypropylmethylcellulose coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose in a mixed organic system of methylene chloride and anhydrous methanol (Sherman, Clark, Lamer, & White, 2002). To avoid the use of toxic organic solvents, at least for outer coating on core pellets, subcoating, an alternative method for reduction of the outer coating load, has been proposed by several researchers, particularly in the patent literature (Lovgren et al., 1988). However, most of the current literature seems to focus on the mechanisms of subcoating used as a barrier between an enteric film coating and an acid labile drug, such as omeprazole, to prevent its degradation (Bergstrand & Wang, 2002; Diane, Koleng, et al., 2003; Diane, Petereit, Beckert, & McGinity, 2003).

In addition to the effect of subcoating on lowering the coating load and shortening the lag time, drug release rates from film-coated dosage forms are also influenced by the

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composition of the pellet core formulation. Octadecanol, a nonbiodegradable fatty alcohol matrix that is insoluble in water, could be used for the preparation of prolonged-release dosage forms with the particular advantage of chemical inertness to other materials (Mine, Evren, & Gökhan, 2006; Otsuka & Matsuda, 1994; Sato, Miyagawa, Okabe, Miyajima, & Sunada, 1997). However, several studies have shown that a higher level of wax matrix is needed to obtain a desired release profile, especially for highly water-soluble drugs like phenylephrin hydrochloride (Hamdani et al., 2002), whereas both extrusion and spheronization are very difficult to control due to an imbalance in the granulating liquid required for proper plasticity of the wet mass, which limits the use of wax matrices. In our study, a comparatively low content of wax matrix was used to control the drug release, mainly by a double-layer membrane to avoid these problems.

In the present study, the in vitro release characteristics of double-layer coated pellets of venlafaxine hydrochloride (VEN) incorporating wax matrices were evaluated in order to obtain an optimized formulation. The objectives of the current research were to investigate the influence of the polymeric subcoating and the matrix material, octadecanol, on the release profile of the extremely water-soluble drug, VEN, from pellets coated with Eudragit® NE30D. Since drug release rates are somewhat dependent on the drug to lipid excipient ratio within the matrix, the drug release from matrix pellets containing the required amount of octadecanol with different doses was also evaluated. It was also our intention to gain further knowledge about the drug release mechanism for this type of drug delivery system. Moreover, the thermal effects associated with octadecanol-based dosage forms also need to be well understood in order to avoid any alterations in drug release during storage.

MATERIALS AND METHODS

Materials

VEN was purchased from Chengdu Kanghong Pharmaceutical Co. Ltd., China. MCC PH101 was purchased from Huzhou Zhanwang Pharmaceutical Co. Ltd., China. Octadecanol was purchased from Shanghai AOKE Chemical Co. Ltd., China. Eudragit® NE30D (methyl methacrylate and ethyl acrylate monomers) was supplied by Röhm Pharma GmbH, Germany. Opadry® I was purchased from Colorcon. All other chemicals were commercial products of reagent grade.

Drug-Excipient Interaction Studies

The possibility of drug-excipient interactions was investigated by differential scanning calorimetry (DSC; TA-60WS, Shimadzu, Japan). The DSC thermograms of pure drug, individual excipients, and drug-excipient mixtures were recorded. The samples were separately sealed in aluminium cells and placed in a thermal analyzer. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/minute over a temperature range of 30°C to 300°C.

Preparation of Drug-Loaded Pellets

A VEN pellet formulation containing 40% w/w VEN and 60% w/w MCC (PH101) was mixed for 15 minutes. Water was added as the granulation liquid to prepare a wet mass, which was then extruded using a Granulator (WL350, Wenzhou Pharmacy Equipment Factory, China) with a 1.2 mm screen on a laboratory scale (1.0 kg). The extrudates were spheronized for 15 minutes in a spheronizer (WL350, Wenzhou Pharmacy Equipment Factory, China) and the beads were dried at 40°C for 24 hours and then sized using 16 to 24 screens.

Pellets were prepared with increasing amounts of 10%, 20%, and 40% w/w VEN containing wax matrix octadecanol of the same size range. Also, for comparison, pellets composed of 10% (w/w) VEN and 90% MCC (PH101) were prepared using the same procedure. The composition of these pellets is shown in Table 1.

Preparation of Polymeric Film Coatings

A 30% w/w dispersion of Eudragit® NE30D was diluted to a final solid content of 15% w/w based on dry polymer weight. Talc was added to the coating dispersion, 50% w/w based on the polymer dry weight. The suspension was equilibrated for at least 30 minutes prior to coating.

The wet mass extruded pellets were subcoated with Opadry® I, which was prepared by adding the polymer to 80% v/v alcohol with a solid content of 8% w/v and using a variable speed mixer (HJ-4, Guohua Group, China) for 45 minutes prior to coating.

All the coating processes were performed using a fluidized bed coater (FD-MP-01, Powrex, Japan) on a laboratory scale (0.5 kg) and under the operating conditions given in Table 2. The coating formulations were stirred throughout the coating process. The outer coated pellets were cured for 24 hours in an oven with an air-circulating fan at 40°C and stored in a desiccator before starting the dissolution studies.

TABLE 1
Composition of Pellets Prepared by Wet Mass Extrusion and Spheronization

	Formulations				
Additive (%) Composition	I	II	III	IV	V
VEN	10	10	10	20	40
Octadecanol	–	20	40	20	20
MCC	90	70	50	60	40

TABLE 2
Polymer Film Coating Processing Conditions

Conditions	Eudragit® NE30D	Opadry® I
Inlet temp (°C)	35	40
Outlet temp (°C)	28–30	35
Spray rate (ml/min)	8	10

Drug Release Studies

In vitro release was studied using a United States Pharmacopeia (USP) XXIII type 1 dissolution test apparatus in purified water for a period of 24 hours. In this, the 900 ml of dissolution medium was kept at 37 ± 0.5°C, and the rotating speed was 100 rpm. The effect of polymer coats and pellet formulation on the release of VEN was studied. Ultraviolet (UV) spectrophotometry was used as the method of analysis and the detection wavelength was 274 nm.

Drug Content Analysis

The samples were assayed by high-performance liquid chromatography (HPLC). Quantities (750 mg) of each batch of coated pellets were weighed accurately and added to a 250-ml volumetric flask containing 180 ml methanol. After 30 minutes of ultrasonic extraction, the solution was diluted with methanol to 250 ml and then passed through a 0.45-μm membrane filter. Precisely 1 ml of this solution was transferred to a 250-ml volumetric flask and water was added to make the volume 250 ml. The sample solution was subjected to HPLC analysis to estimate the VEN content. The HPLC system (HITACHI D-7000) involving a C18 column (5 μm, 4.6 × 150 mm; Diamonsil) consisted of an autosampler (L-7200), two pumps (L-7100), and a UV detector (L-7420), all interfaced with D-7000 HSM software. For the analysis of the VEN content, the mobile phase used was acetonitrile water (20:80) containing 0.1% triethylamine (pH 3.0) with a flow rate of 1.0 ml/minute, and the UV detector was set at 226 nm.

Scanning Electron Microscopy (SEM)

The surface and cross-section of the pellets were scattered on mutually conductive double-sided adhesive tape placed on an aluminum stub and gold-coated using a JFC-1200 Fine Coater (JEOL, Japan) with a current of 20 mA for 200 seconds. Scanning electron micrographs were imaged with an SEM (SSX-550, Shimadzu, Japan) at an accelerating voltage of 15 KV and with an emission current of 170 μA by scanning fields randomly at several suitable magnifications.

RESULTS AND DISCUSSION

Influence of Eudragit® NE30D Coating on Drug Release

The core pellets containing 40% w/w VEN and 60% w/w MCC were coated only with Eudragit® NE30D at different coating levels based on theoretical weight gains of 10%, 20%, 30%, and 40%. Drug release from coated pellets to a great extent depends on the coating levels of the polymeric dispersion applied on the core pellets as shown in Figure 1. The dissolution data of Eudragit® NE30D coated pellets can be described by the Higuchi model according to regression coefficient result. The lag time was calculated as the x-axis intercept for zero drug release, from the linear part of the dissolution profile (15%–70% drug release). A faster release was observed with a 20% coating level compared with a 40%, which indicated that there was an inverse relationship between the thickness of the polymer coat and the rate of drug release. On the other hand, it was found that the lag time required for the initiation of drug release became longer as the coating thickness increased. Drug release was initiated after a 0.8 hours and 1.8 hours lag time at 30% and 40% coating levels, respectively. In addition, the coating process was found to be difficult to control due to intermittent adherence, which resulted in irregularities on the surface of the pellets. This might be attributed to migration of the highly water-soluble VEN into the aqueous film coating during film application, where presence of the drug may lead to pore formation during dissolution and, hence, higher coating levels being needed (Rahman & Yuen, 2005). In addition, there was no evidence of an interaction between drug and Eudragit® NE30D resulting in the need for a high coating level to obtain a satisfactory dissolution profile during the preliminary differential scanning calorimetry studies. Therefore, a seal coat or subcoat was considered to improve the coating process and the drug release characteristics by reducing the migration of drug to polymer film to reduce the coating load and controlling the lag time (Diane, Koleng, et al., 2003).

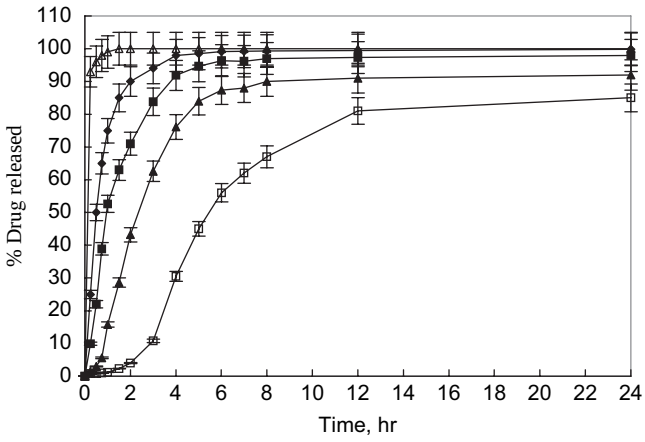


FIGURE 1. Influence of different coating levels on in vitro venlafaxine HCl release from the core pellets composed of 40% VEN and 60% MCC coated with Eudragit® NE30D alone in purified water at 37°C at 100 rpm for 24 hours: (✦) 10% polymer weight gain, (■) 20% polymer weight gain, (▲) 30% polymer weight gain, (□) 40% polymer weight gain, and (△) uncoated pellets.

Influence of Double-Layer Polymeric Coating on Drug Release

Since VEN is slightly soluble in alcohol, the alcohol solvent polymer system was used for seal coating. Alcohol-soluble Opadry® I was selected as a polymeric subcoat for further study to generate a desired release profile. Also, the commercial product equivalent to VEN 75 mg in the form of extended-release pellets was used as a reference, with the dissolution test standard: less than 30% drug release in 2 hours, 30% to 55% in 4 hours, 55% to 80% in 8 hours, 65% to 95% in 12 hours, and not less than 80% in 24 hours. Moreover, drug release should initiate within 1.0 hour according to the data calculated from the dissolution profile, which provides 24-hour therapeutic blood levels of the drug. In order to investigate the influence of double-layer coating on drug release properties and, particularly, the influence of the subcoat Opadry® I on the reduction of outercoat Eudragit® NE30D weight gain, the amount of VEN released in purified water for 24 hours from different coating levels and the composition of coating formulations with core pellets composed of 40% w/w VEN and 60% w/w MCC were studied, as shown in Table 3. The release rates K of the fits of VEN release data to different kinetic models for formulations A through E are shown in Table 4. In order to reduce the influence of lag time and declining rate phase on the fits of the kinetic models, the data between 15% and 70% were used for modeling drug release. The lag time t_{lag} for pellets coated with double-layer coats was calculated from the x-axis intercept when the amount of drug released was zero. Correlation coefficients R^2 of the fits of VEN release data to different kinetic models are also shown in Table 4. The correlation coefficients for the best statistical fits reveal that the Higuchi/square root time model is probably the most suitable model for all the release data, suggesting that diffusion is a rate-limiting step in the release (Ritger & Peppas, 1987).

Figure 2 shows the plots of the release of VEN from pellets coated with 6%, 8%, and 10% Opadry® I at the equivalent 12% Eudragit® NE30D outercoating (formulations A, C, and E). A faster initial release was observed with 6% compared with 10% Opadry® I coating levels: 34.6% and 9.8% of VEN release in 2 hours, respectively. Obviously, the seal effect on migration of VEN to polymer Eudragit® NE30D increased with increasing thickness of Opadry® I. However, the release rate of 10% Opadry® I–coated pellets and the percentage drug release from pellets were both increased and even more than the data at 6% and 8% coating levels at the end of dissolution. This might be due to the composition of Opadry® I which consists of approximately 91% w/w hydroxypropyl methylcellulose (E-6) and 9% w/w polyethylene glycol (Porter & Woznicki, 1985). At the initial stage of dissolution, a higher Opadry® I level resulted in a longer diffusion path length for drug release, and the lag time for the initial drug release was thereby increased. As water influx into the seal layer increased, Hydroxypropylmethylcellulose (HPMC) hydrated and formed a gel, leading to the increasing subcoat thickness (Sadeghi, Ford, Rubinstein, & Rajabi-Siahboomi, 2000). Therefore the increasing subcoat thickness might increase the tensile stress over the outercoating membrane, thereby increasing the permeability of the dissolved drug molecules, which even overcame the diffusion barrier of the seal coats, and finally, increased the drug release rate. With the greater HPMC erosion in the oversubcoat formulation during the dissolution test, the increased pore formation on the subcoat might increase the porosity within the pellets and facilitate drug dissolution. The latter would consequently increase the extent of drug release from the pellets. SEM of a cross-section of pellets coated with 8% Opadry® I subcoating and 12% Eudragit® NE30D outercoating showed a thin coating layer after 8 hours in the

TABLE 3
Coating Composition and Coating Levels of Core Pellets with 40% w/w VEN and 60% w/w MCC

	Coating Formulations				
Coating Level (%)	i	ii	iii	iv	v
Opadry® I	6	8	8	8	10
Eudragit® NE30D	12	9	12	15	12

TABLE 4
Drug Release Rate Constants K and Correlation Coefficients R^2 Obtained from Data Corresponding to 15% to 70% for Formulation A through E

		Formulation				
Model		i	ii	iii	iv	v
Zero-order	K (%·h^{-1})	18.6	20.1	13.3	8.6	11.6
	R^2	0.9775	0.9751	0.9837	0.992	0.9951
Square root	K (%·h$^{-1/2}$)	60.7	65.5	52.8	39.6	48.6
	R^2	0.9923	0.9911	0.9917	0.9975	0.9991
First-order	K (h^{-1})	0.45	0.52	0.26	0.24	0.24
	R^2	0.9202	0.9008	0.9631	0.9178	0.9692

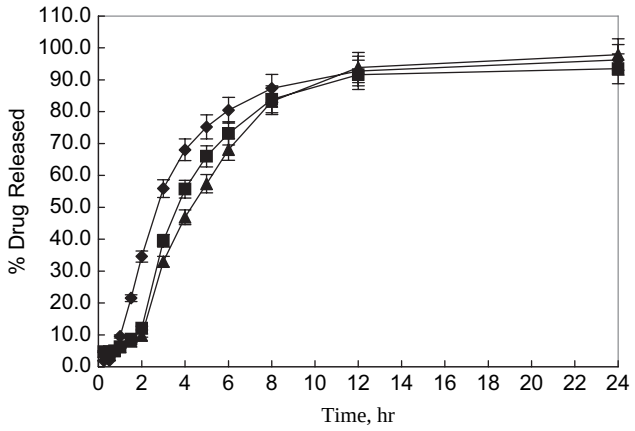


FIGURE 2. Effect of Opadry® I subcoating loads on the drug release of pellets composed of 40% (w/w) VEN and 60% (w/w) MCC coated with 12% Eudragit® NE30D outercoating: (✦) 6% polymer weight gain, (■) 8% polymer weight gain, and (▲) 10% polymer weight gain.

dissolution test shown in Figure 3, which might explain the leakage of the Opadry® I coating film undergoing the dissolution test.

Figure 4 shows the plots of the release of VEN from pellets coated with 9%, 12%, and 15% Eudragit® NE30D at the equivalent 8% Opadry® I subcoating (formulations B, C, and D). Similar to pellets coated only with Eudragit® NE30D, the amount of VEN release was reduced at each coating composition as the Eudragit® NE30D coating loads increased. At a high coating load of 15%, only about 4% and 47% of VEN was released in 2 hours and 6 hours, respectively, whereas those pellets coated to weight increases of 12% and 9% released about 12% and 32% in 2 hours and 73% and 83% in 6 hours, respectively. After examining the coated surface of both pellet types using SEM, it was found that the surface of the pellets coated with 15% Eudragit® NE30D was comparatively smoother than that of pellets with a 12% coating level as shown in Figure 5. This might be due to the continuous layering of coating material on the surface of the pellets as more layers of film are applied and, hence, the holes from overlapping films are gradually blocked, leading to a reduction in dissolution rate. However, much less drug was released from pellets with double-layer coats compared with that of pellets coated with Eudragit® NE30D alone at the equivalent total coating loads. The release rate from formulation C was three times slower than for pellets coated with Eudragit® NE30D alone at the 20% coating load. At the equivalent 20% total coating level, more than 90% VEN was released from pellets with the seal coat Opadry® I after 12 hours, whereas it was 4 hours for the formulation with Eudragit® NE30D coating alone, indicating the marked effect of Opadry® I subcoats on reducing the Eudragit® NE30D coating level by reducing drug migration into outer coats.

The drug release from pellet formulations coated with 8% Opadry® I and 12% Eudragit® NE30D (formulation C) was found to be a little faster than commercial product (55%) in

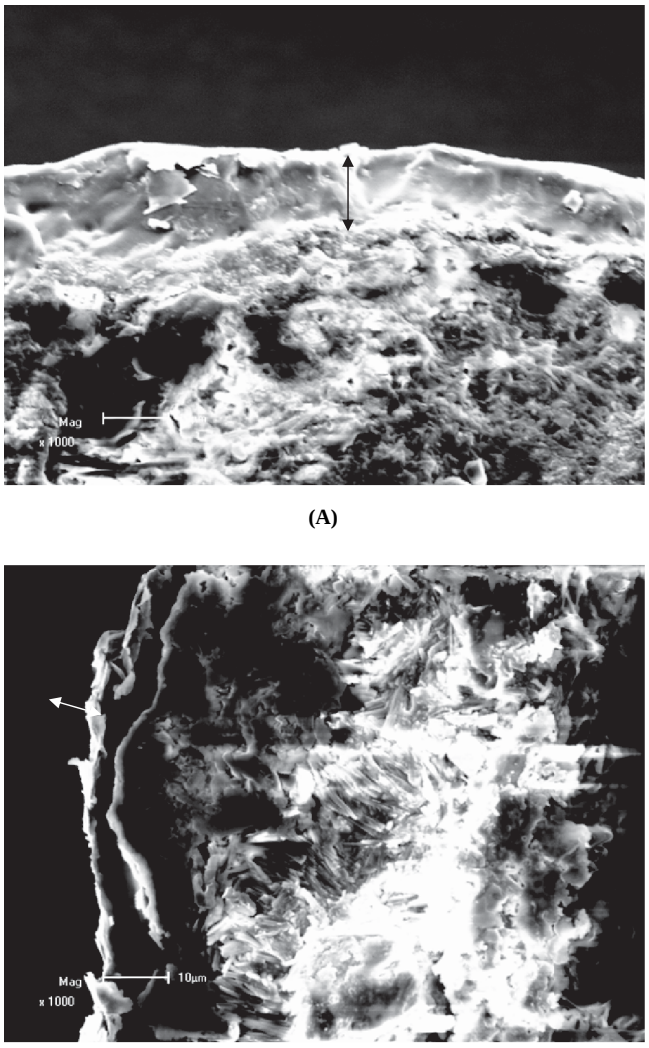


FIGURE 3. Micrographs of cross-sections of VEN pellets coated with 8% Opadry® I subcoating and 12% Eudragit® NE30D outercoating (formulation C; magnification ×1000): (A) before dissolution and (B) after 8 hours dissolution. (←→) = double-layer coats.

4 hours, whereas there was an unacceptable lag time (1.3 hours) for drug release from these pellets with an additional 3% Eudragit® NE30D to 15% coating load (formulation D). Furthermore, for optimizing products, a portion of the uncoated pellets or pellets with a lower coating level had to be added to the batch (formulation D) to provide, after thorough mixing, a loading dose for a rapid increase of initial release, which increased the complexity of the production process. Alternatively, a shorter lag time could be obtained by using a mixture of polymer film and a small amount of drug or water-soluble substrate (Rahman & Yuen, 2005), which might not be suitable for a highly water-soluble drug (Li, Mehta, Buehler, Grim, & Harwood, 1990), such as VEN. Although it is a complex manufacturing process, adding another layer containing

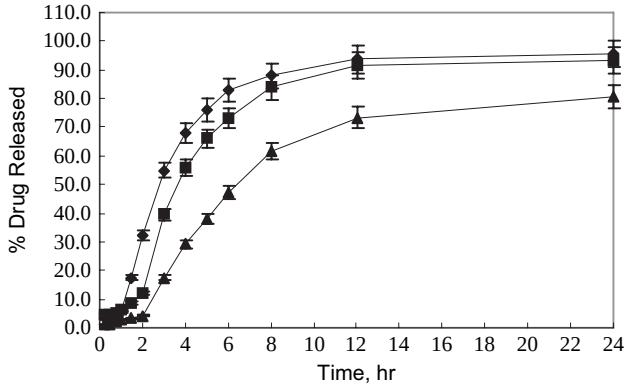


FIGURE 4. Effect of Eudragit® NE30D outercoating loads on the drug release of pellets composed of 40% (w/w) VEN and 60% (w/w) MCC coated 8% weight gain of Opadry® I subcoating: (✦) 9% polymer weight gain, (■) 12% polymer weight gain, and (▲) 15% polymer weight gain.

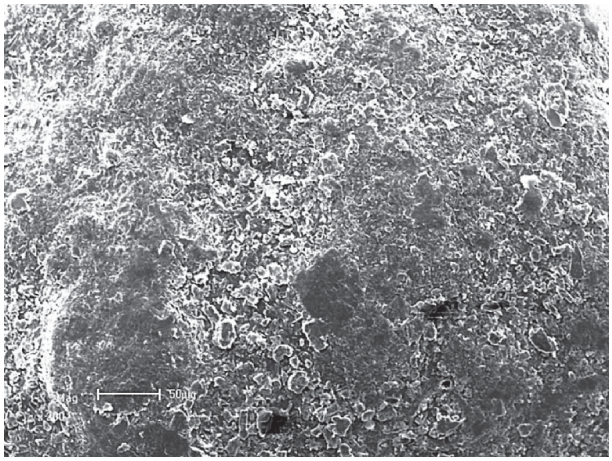
drugs may also allow faster onset of drug release as a loading dose (Allen, Allen, Popovich, & Ansel, 2005). In our study, a fatty alcohol, octadecanol, was added to pellet formulations to modify the release of drugs from systems coated with double-layer polymers (8% Opadry® I and 12% Eudragit® NE30D) and to shorten the lag time by applying a comparatively lower coating load to obtain a satisfactory release rate.

Influence of Pellet Formulation on Drug Release

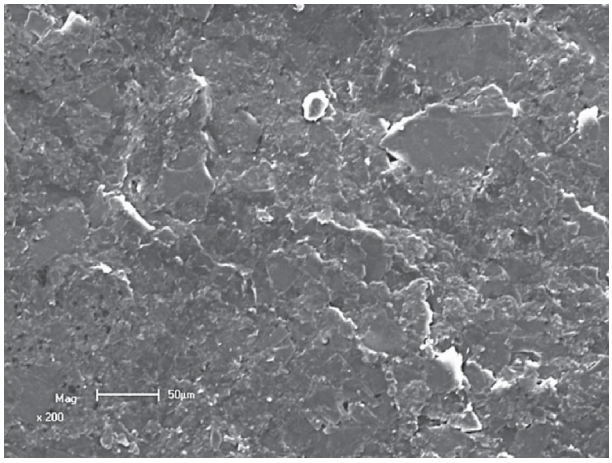
Instead of using a higher coating level leading to a longer lag time, the octadecanol was incorporated into core pellet formulations to improve the drug release characteristics. To examine the effect of octadecanol on drug release profiles, pellets were prepared containing different amounts of octadecanol and VEN. The composition of the different formulations is shown in Table 1.

Influence of Octadecanol Amount Within Matrix Pellets on Drug Release

An increasing amount of 0%, 20%, and 40% octadecanol was added to 10% (w/w) VEN core pellets (formulations I, II, and III in Table 1). The release profiles of VEN from those pellets coated with 8% Opadry® I and 12% Eudragit® NE30D are shown in Figure 6. The total amount of VEN release decreased as the amount of octadecanol in core pellets increased. The release rates K and correlation coefficients R^2 of the fits of release data to the different kinetic models are shown in Table 5. The lag time t_{lag} for pellets with double-layer coats was also calculated from the x-axis intercept when the amount of drug released was zero. The lag time increased and the rate of drug release decreased upon increasing the lipid excipient content within the matrix pellets, irrespective of the kinetic model used. The reduction in release rate accompanied by the increasing octadecanol amount may be due to the reduced drug dissolution from the sustained-release pellets by incorporating



(A)



(B)

FIGURE 5. Micrographs of VEN pellets coated with different Eudragit® NE30D coating weights at 8% Opadry® I subcoating load (magnification × 200): (A) 12% w/w Eudragit® NE30D coating load and (B) 15% w/w Eudragit® NE30D coating load.

VEN into the inert water-insoluble wax matrix material, octadecanol. However, as the percentage of octadecanol was increased up to 40%, the drug release kinetic model changed from the Higuchi to the zero-order model, which provided the best fit for the data. According to Ford and colleagues (1991) and Ritger and Peppas (1987), to evaluate the mechanism of drug release, dissolution data need to be analyzed using Equation 1, in which Q is the percentage of drug released at time t, K is the release rate constant, t_{lag} is the lag time, and n is the release exponent indicating the mechanism of drug release. The Higuchi and zero-order models may be special cases of Equation 1

$$Q = K(t - t_{lag})^n \quad (1)$$

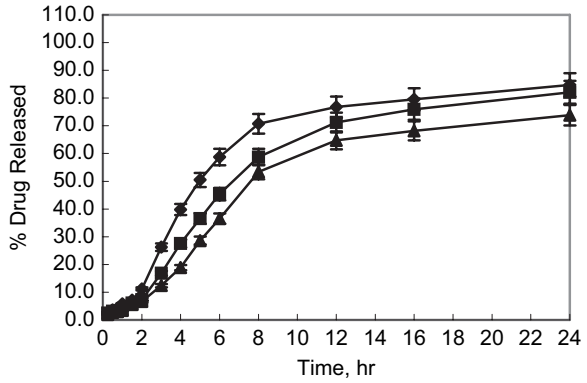


FIGURE 6. Influence of different octadecanol contents within 10% (w/w) VEN core pellets coated with 8% weight gain Opadry® I subcoating and 12% weight gain Eudragit® NE30D outercoating on drug release in purified water at 37°C at 100 rpm for 24 hours: (✦) without octadecanol, (■) 20% octadecanol, and (▲) 40% octadecanol.

where $n = 0.5$ and $n = 1$, indicating that diffusion or dissolution is the predominant mechanism controlling the release of drug from pellets, respectively. At 40% octadecanol, due to the increased difficulty of drug dissolution from the core pellets, diffusion of drug through the polymeric coat film seems not to be a major rate-limiting step in the release process; therefore, the rate of dissolution of the drug particles largely controls the release mechanism. Since the higher content with 40% octadecanol seems to provide a significant effect on release characteristics, especially an unacceptable lag time of about 1.5 hours and less than 75% release in 24 hours, the formulation containing 20% octadecanol in the matrix that might lower the amount of double-layer coats required by reducing the release rates, was selected for further study.

Influence of VEN Content Within Matrix Pellets on Drug Release

The dissolution profiles of different drug contents within 20% (w/w) octadecanol matrix pellets coated with 8% weight gain Opadry® I subcoating and 12% weight gain Eudragit® NE30D outercoating (formulations II, IV, and V in Table 1) are shown in Figure 7. Increasing the VEN content increased with the amount of drug release. The release rates K and correlation coefficients R^2 of the fits of release data to the different kinetic models are also shown in Table 5. The lag time t_{lag} for pellets with double-layer coats was also calculated, as described above. At a drug content of 10% and 40%, the drug release rate from pellets increased from about 38.3 to 48.7, while the lag time decreased from about 1.3 to 0.8 hours. This is probably explained by the different osmotic effects depending on the amount of soluble drug. The high drug content formulation is expected to induce a higher osmotic influx rate of water into the pellet and, at the same time, produce a more rapid expansion of the surrounding membrane. Another effect that may contribute to the different lag times is the tensile stresses in a membrane of the present type, which have been shown to increase the permeability of dissolved drug molecules (Hjärtstam, Borg, & Lindstedt, 1990). The correlation coefficients R^2 for the best statistical fits revealed that the Higuchi kinetic model is probably the model most applicable to all the release data. In the comparison of different drug contents (formulations II, IV, and V), it was observed that the drug content within matrix pellets had no apparent effect on the Higuchi kinetics of drug release. In the case of formulation V where the pellets were loaded with 40% w/w VEN coated with a double-layer coating system containing 20% lipid matrix, the drug release profile satisfied the dissolution test compared with commercial product providing a sustained-release profile, following Higuchi release kinetics with an r value of 0.995.

Influence of Thermal Treatment on Drug Release

After the pellets subcoated with Opadry® I were stored at 40°C for 24 hours, the Eudragit® NE30D coating process was difficult to carry out since the pellets were defluidized due to the electrostatic charges that had developed on the surface of the pellets. So the subcoated pellets were not suitable for storage at high temperatures for long periods.

The optimized formulation V was chosen for the stability study. The drug release of coated pellets initially and after

TABLE 5
Drug Release Rate Constants K and Correlation Coefficients R^2 Obtained from Data Corresponding to 15% to 70% for Formulation I through V

		Formulation				
Model		I	II	III	IV	V
Zero-order	K (%·h^{-1})	10.8	8.3	8.3	9.0	11.6
	R^2	0.9883	0.9897	0.9982	0.9792	0.9935
Square root	K (%·h$^{-1/2}$)	45.5	38.3	38.0	41.4	48.8
	R^2	0.9967	0.9992	0.9896	0.995	0.9966
First-order	K (h^{-1})	0.27	0.24	0.18	0.21	0.26
	R^2	0.9516	0.9177	0.8358	0.913	0.9644

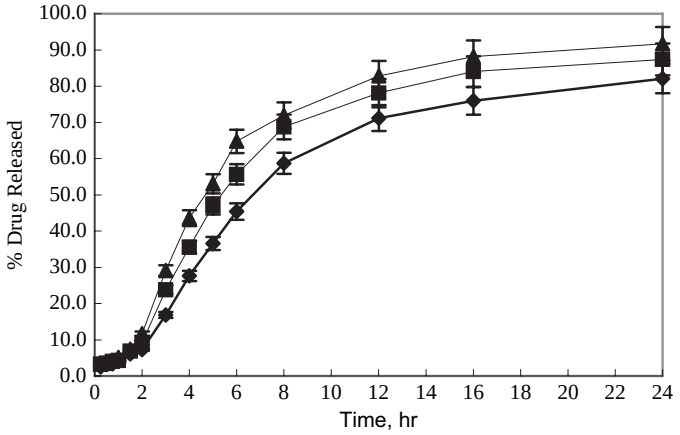


FIGURE 7. Influence of different drug contents within 20% (w/w) octadecanol matrix pellets coated with 8% weight gain Opadry® I subcoating and 12% weight gain Eudragit® NE30D outercoating on drug release in purified water at 37°C at 100 rpm for 24 hours: (✦) 10% VEN, (■) 20% VEN, and (▲) 40% VEN.

1 month of storage at 40°C in an oven indicated a negligible change in the dissolution profiles, which still satisfied the dissolution standard: less than 30% drug release in 2 hours, 30% to 55% in 4 hours, 55% to 80% in 8 hours, 65% to 95% in 12 hours, and not less than 80% in 24 hours, and the rate of drug release seemed to be stable during storage.

CONCLUSIONS

In this study, the VEN wax matrix sustained-release pellets with double-layer coatings were developed to obtain a satisfactory profile for once-daily sustained release. The polymeric subcoat Opadry® I played an important role in preventing migration of the highly water-soluble drug into the outer coating and, thus, avoided the use of a toxic organic solvent, at least for the outer coating. Incorporation of a comparatively lower amount of octadecanol into the pellet core was effective in retarding drug release. However, as the amount of octadecanol increased, the mechanism tended to be dissolution-controlled release. The high dose VEN pellets might to some extent overcome the longer lag time, which was used for the production of matrix pellets. In the optimized formulation V, the 40% VEN wax matrix core pellets containing 20% octadecanol with relatively lower coating levels (8% Opadry® I and 12% Eudragit® NE30D), allowed a faster onset of drug release within about 1 hour, a suitable rate for prolonged drug release, and comparatively complete release of more than 90% in 24 hours, and these were found to be stable during storage.

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REFERENCES

Allen, L. V., Allen, J., Popovich, N. G., & Ansel, H. C. (2005). *Ansel's pharmaceutical dosage forms and drug delivery systems* (8th ed.). Philadelphia: Lippincott Williams & Wilkins.

Bergstrand, P., & Wang, P. (2002). *Pharmaceutical formulation comprising omeprazole*. U.S. Patent 6428810.

Diane, B. L., Koleng, J. J., & McGinity, J. W. (2003). The influence of polymeric subcoats and pellet formulation on the release of chlorpheniramine maleate from enteric coated pellets. *Drug Dev. Ind. Pharm., 29*, 909–924.

Diane, B. L., Petereit, H., Beckert, T., & McGinity, J. W. (2003). Properties of enteric coated sodium valproate pellets. *Int. J. Pharm., 264*, 85–96.

Ford, J. L., Mitchell, K., Sawh, K., Ramdour, S., Armstrong, D., & Elliott, P. N. C., et al. (1991). Hydroxypropylmethylcellulose matrix tablets containing propranolol hydrochloride and sodium dodecyl sulphate. *Int. J. Pharm., 71*, 213–221.

Ghebre-sellassie, I., Gordon, R. H., Nesbitt, R. U., & Fawzi, M. B. (1987). Evaluation of acrylic-based modified-release film coatings. *Int. J. Pharm., 37*, 211–218.

Göran, F., Åsa, T., & Göran, A. (2003). Modelling of drug release from coated granular pellets. *J. Control. Release, 92*, 113–123.

Hamdani, J., Moës, A. J., & Amighi, K. (2002). Development and evaluation of prolonged release pellets obtained by the melt pelletization process. *Int. J. Pharm., 245*, 167–177.

Heng, P. W. S., Hao, J., Chan, L. W., & Chew, S. H. (2004). Influences of osmotic agents in diffusion layer on drug release from multilayer coated pellets. *Drug Dev. Ind. Pharm., 30*, 213–220.

Hjärtstam, J., Borg, K., & Lindstedt, B. (1990). The efect of tensile stress on permeability of free films of ethyl cellulose containing hydroxypropyl methylcellulose. *Int. J. Pharm., 61*, 101–107.

Li, S. P., Feld, K. M., & Kowarski, C. R. (1997). The effect of polymer coating systems on the preparation, tableting and dissolution properties of sustained-release drug pellets. *Drug Dev. Ind. Pharm., 23*, 623–631.

Li, S. P., Mehta, G. N., Buehler, J. D., Grim, W. M., & Harwood, R. J. (1990, April). The effect of film-coating additives on the in vitro dissolution release rate of ethyl cellulose-coated theophylline granules. *Pharmaceutical Technology International*, 48–52.

Lovgren, K., I., Pilbrant, A., G., Yasumura, M., Morigaki, S., Oda, M., & Ohishi, N. (1988). *Pharmaceutical preparation for oral use*. U.S. Patent 4786505.

Mine, Ö., Evren, H., & Gökhan, E. (2006). Release and diffusional modeling of metronidazole lipid matrices. *Eur. J. Pharm. Biopharm., 63*, 331–339.

Otsuka, M., & Matsuda, Y. (1994). Effect of cogrinding time on the release of pentoxyfylline from waxy matrix tablets. *J. Pharm. Sci., 86*, 929–934.

Ozturk, A. G., Ozturk, S. S., Palsson, B. O., Wheatley, T. A., & Dressman, J. B. (1990). Mechanism of release from pellets coated with an ethylcellulose-based film. *J. Control. Release, 14*, 203–213.

Porter, S. C., & Woznicki, E. J. (1985). *Dry edible film coating composition, method and coating form*. U.S. Patent 4543370.

Rahman, N. U., & Yuen, K. H. (2005). Eudragit NE40-drug mixed coating system for controlling drug release of core pellets. *Drug Dev. Ind. Pharm., 31*, 339–347.

Rekhi, G., Porter, S., & Jambhekar, S. (1995). Factors affecting the release of propanolol hydrochloride from beads coated with aqueous polymeric dispersions. *Drug Dev. Ind. Pharm., 21*, 709–729.

Ritger, P. L., & Peppas, N. A. (1987). A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. *J. Control. Release, 5*, 37–42.

Sadeghi, F., Ford, J. L., Rubinstein, M. H., & Rajabi-Siahboomi, A. R. (2000). Comparative study of drug release from pellets coated with HPMC or surelease. *Drug Dev. Ind. Pharm., 26*, 651–660.

Sato, H., Miyagawa, Y., Okabe, T., Miyajima, M., & Sunada, H. (1997). Dissolution mechanism of diclofenac sodium from wax matrix granules. *J. Pharm. Sci., 86*, 929–934.

Sherman, D. M., Clark, J. C., Lamer, J. U., & White, S. A. (2002). *Extended release formulation of venlafaxine hydrochloride*. U.S. Patent 6419958.

Umprayn, K., Chitropas, P., & Amarekajorn, S. (1999). Development of terbutaline sulfate sustained-release coated pellets. *Drug Dev. Ind. Pharm., 25*, 477–491.