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Research Article

Optimization and *In vivo* Pharmacokinetic Study of a Novel Controlled Release Venlafaxine Hydrochloride Three-Layer Tablet

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Abstract. Several matrix tablet formulations (hydrophilic-based, wax-based, and three-layer tablets) were designed for controlling the release of the highly water soluble drug, venlafaxine hydrochloride (VenHCl) for once-daily administration. The three-layer tablets consist of non-swellable, compritol-based middle layers containing the drug to which hydrophilic top and bottom barrier layers were applied. A 2^3 full-factorial design was employed for optimization and to explore the effect of different variables on the release rate of the drug from the three-layer tablets. The optimized levels of each independent variable were based on the criterion of desirability. The calculated values of f_1 and f_2 were 4.131 and 79.356, respectively; indicating that the release profile of the optimized PEO layered tablet formulation is comparable to that of the target release model. The pharmacokinetic parameters of VenHCl from the optimized three-layer tablet was compared to the marketed extended release capsule as a reference in healthy human subjects using a randomized crossover design. In this study, the 90% confidence interval for AUC_{0-24} and $AUC_{0-\infty}$ are within (0.8–1.25), which satisfied the bioequivalence criteria. It could be concluded that a promising once-daily extended-release three-layer tablet of the highly water soluble drug, VenHCl, was successfully designed.

KEY WORDS: controlled release; factorial design; optimization; pharmacokinetic; three-layer tablet; venlafaxine.

INTRODUCTION

Venlafaxine hydrochloride (VenHCl) is atypical antidepressant that is a strong inhibitor of serotonin and noradrenaline reuptake and a moderate inhibitor of dopamine reuptake (1). It is a white crystalline solid freely soluble in water (534 mg/ml) (2). The recommended dose of VenHCl is 75 to 450 mg/day (3). The steady-state half lives of venlafaxine and its active metabolite, *o*-desmethylvenlafaxine, are 5 and 11 h, respectively, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of the drug (4). The short half life of the drug indicates the need for controlled release dosage form. Moreover, the use of extended release formulation is associated with less nausea and dizziness during treatment with VenHCl (3). VenHCl is currently available as an extended release capsule, containing VenHCl equivalent to venlafaxine 75 mg in the form of coated pellets for a once daily administration under the brand name of Effexor®XR. The major disadvantages of coating methods are their low productivity, long processing time, high cost, and variation between and within batches (3).

Generally, the most common controlled delivery system has been the matrix type such as tablets, where the drug is uniformly dissolved or dispersed throughout the polymer because of low cost and ease of manufacturing. However, their release behavior is inherently nonlinear in nature as a result of decreasing release rate with time (5). Thus, various matrix designs have been recommended to achieve an almost constant release rate of the drug with time. One of these techniques depends on the use of multilayered matrix tablets as drug delivery devices. A multilayer system consists of a matrix core, containing a solid dispersion of active ingredient with waxy substance, and polymeric barrier layers applied on both faces of the core during tabletting (6). Compritol® 888 ATO and Precirol® ATO 5 are composed of glyceryl behenate and glyceryl palmitostearate, respectively. Their waxy lipophilic properties and low fusion point make them ideal retardant materials for sustained release dosage forms of highly water soluble drugs.

In this investigation, the barrier layers contain hydrophilic polymers such as polyethyleneoxide (PEO) or hydroxypropylmethylcellulose (HPMC). The drug release mechanism from multilayered matrix tablets involves the following sequence. In the initial stage, the top and bottom layers applied to the wax-based core matrix are able to obstruct the contact of the matrix tablet with the dissolution medium by limiting the solvent penetration rate and by reducing the surface available for drug release. Thus, the burst effect can be controlled and the drug release occurs from the lateral surface. Throughout the dissolution, top and bottom hydrophilic barrier layers swell and erode where the surface available for drug release increases. Hence, the

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decrease of the release rate due to the reduction of drug concentration gradient is compensated by the simultaneous increase in the available area for drug diffusion and release, resulting in nearly linear release profile (7, 8).

The aim of this study was the development of zero-order controlled release formulations of a highly water soluble drug, VenHCl, using a simpler method, three layer tablet technology, than the coating method used for preparing the pellets of the marketed product. A 2^3 full-factorial design was employed for optimization and to explore the effect of the compression force, amount of the hydrophilic barrier layers, and the % of hydrophilic polymers in the barrier layers on the release rate of the drug. The percentage drug released at a predetermined times were selected as dependent variables. *In vivo* pharmacokinetic studies were carried out for the optimized formulation and compared with the reference marketed formulation.

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride was kindly obtained from SIGMA Pharmaceutical Industries (Egypt) HPMC (METHOCEL™ K100M, Dow Chemical Company, Midland, USA), PEO (Mol.Wt. 7,000,000, Aldrich Chemical Co. USA) were used as the hydrophilic barriers. Compritol® 888 ATO and Precirol® ATO 5 were kindly supplied from Gattefossé (Saint Priest, France). Hydrochloric acid and tribasic sodium phosphate were provided by Merck (Darmstadt, Germany). Acetonitrile and other HPLC solvents (HPLC grade) were obtained from Sigma Chemical Company (USA).

Methods

Drug–Excipient Compatibility Studies

The compatibility of drug–excipient was investigated by differential scanning calorimetry. The DSC thermograms of pure drug, individual excipients, and drug–excipient mixtures (1:1 *w*/*w*) were recorded. The samples were separately sealed in aluminum cells and set in a Shimadzu thermal analyzer (Shimadzu DSC 60, TA-60 WS, Japan) under dynamic nitrogen atmosphere. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30–250°C.

Preparation of HPMC-Based Hydrophilic Matrix Tablet of VenHCl

Tablets were prepared by direct compression. Physical blends of VenHCl and HPMC in ratios 1:1, 1:2, and 1:4 were mixed with mortar and pestle for 15 min. Then, the mixtures were compressed with hydraulic press (Shimadzu, Japan) equipped with a compression set having a diameter of 13 mm, under compression force of 2 tons for 15 s.

Preparation of Wax-Based Matrix Tablet of VenHCl

In order to attempt to decrease VenHCl dissolution rate, fatty materials, Compritol® and Precirol®, were used in the form of solid dispersion or physical mixture with the drug. The physical mixture or solid dispersion were mixed with other additives then directly compressed as previously mentioned. The tablet weight was adjusted to 250 mg using lactose as diluent. Table I depicts the composition of the prepared tablets.

In preparation of the solid dispersion, Compritol or Precirol was melted in porcelain evaporating dish by water bath at 75°C. VenHCl was added with continuous stirring to get a homogeneous dispersion. Then, the molten mass was allowed to cool down and solidify. Subsequently, the mass was ground and pulverized. The obtained powders were stored in a desiccator at room temperature until use.

Physical mixtures were prepared to compare and elucidate the sustained-release effect of solid dispersion matrices. Different ratios of VenHCl to Compritol® or Precirol® were directly mixed with mortar and pestle for 15 min. The resulting mixtures were then stored in a desiccator at room temperature until use.

Preparation of Three-Layer Matrix Tablet of VenHCl Using 2^3 Full-Factorial Design

The three-layer tablet was designed to be composed of the following layers: the top and bottom layers composed of HPMC or PEO that was dry mixed with lactose and a middle wax-based matrix composed of a solid dispersion of VenHCl to compritol in ratio 1:1.25 containing 84.86 mg of VenHCl equivalent to 75 mg Venlafaxine. The ingredients of bottom layer were placed in the die and precompressed at 0.5 ton. Then, the ingredients of the middle layer were added and precompressed at 0.5 ton. Finally, the ingredients for the top layer were added, and the whole assemblage was compressed at compression force of 2 or 4 tons with a dwell time of 15 s.

For each hydrophilic polymer, either HPMC or PEO, a 2^3 randomized full-factorial design was used in order to investigate the joint influence of three formulation variables using Minitab® software. In this design, three factors are evaluated, each at two levels, and experimental trials are performed at all eight possible combinations. The compression force (X_1), the percentage of the hydrophilic polymer in the hydrophilic layer (X_2), and amount of the hydrophilic layer (X_3) were selected as independent variables (Table II). The cumulative percentage of drug released at 1,

Table I. Composition of Wax-Based Matrix Tablet of VenHCL

Formula code	Method of preparation	Fatty material	VenHCL–fatty material ratio	Diluent (lactose) mg
C1	SD	Compritol	1:1	80
C2	PM	Compritol	1:1	80
C3	SD	Precirol	1:1	80
C4	PM	Precirol	1:1	80
C5	SD	Compritol	1:1.75	16.64
C6	PM	Compritol	1:1.75	16.64
C7	SD	Precirol	1:1.75	16.64
C8	PM	Precirol	1:1.75	16.64
C	SD	Compritol	1:1.25	59

VenHCL weight: 84.86 equivalent to 75 mg Venlafaxine
SD solid dispersion, *PM* physical mixture

Table II. Full-Factorial Design Used to Optimize the Formulation

Factor	Level used	
	−1	1
X_1: Compression Force (tons)	2	4
X_2: % of Hydrophilic polymer weight in the hydrophilic layer weight (%)	33	66
X_3: Amount of hydrophilic layer (mg)	150	240
Response	Constraints	
Y_1: Cumulative % drug released at 1 h	$18\% \le Y_1 \le 22\%$	
Y_6: Cumulative % drug released at 6 h	$42\% \le Y_6 \le 51\%$	
Y_{12}: Cumulative % drug released at 12 h	$71\% \le Y_{12} \le 86\%$	

6, and 12 h (Y_1, Y_6, and Y_{12}, respectively), were selected as dependent variables. Table III depicts the composition of the prepared tablets.

In vitro Release of VenHCl

The release characteristics of VenHCl from the prepared formulations were determined according to the USP dissolution II paddle method at a rotation speed of 50 rpm in 1,000 ml of dissolution medium at 37±0.5°C using a dissolution tester (Pharma Test Dissolution Tester, Germany). The dissolution test media used were as follows: 750 ml of 0.1 N hydrochloric acid (pH1.2±0.1) for 2 h followed by addition of 250 ml of 0.2 M tribasic sodium phosphate to raise the pH to be 6.8±0.1 (9). Dissolution samples (5 ml) were collected at predetermined time intervals. Immediately after each sample withdrawal, a similar volume of fresh medium was added to the dissolution medium to maintain the volume in the vessel constant. Collected samples were filtered through 0.45-μm Millipore filters. The concentration of VenHCl in samples was spectrophotometrically determined at 276 nm using a UV spectrophotometer (UV 160 1 PC UV-Visible, Shimadzu, Japan). Cumulative percentage of drug released from the tablets were calculated and plotted as a function of time.

Kinetic Analysis of the Release Data

The mean *in vitro* drug release data were fitted to different kinetic models (zero order (10), Higuchi (11, 12), and Korsemeyer–Peppas (13, 14)) to evaluate the kinetics of drug release from the prepared matrices. The large value of the coefficient of determination (R^2) indicated a superiority of the dissolution profile fitting to mathematical equations.

Swelling and Erosion Studies

Matrix swelling and erosion studies were performed according to the method published by Roy *et al.* (15). The standard USP/NF dissolution apparatus I (Pharma Test Dissolution Tester, Germany) was used for this purpose. The optimized formulation was weighed, placed in dissolution baskets, and subjected to dissolution in 900 ml of water at 37° C with the baskets rotating at 50 rpm. At regular intervals, basket-formulation assembly was removed from the dissolution vessels and weighed then dried to a constant weight in a hot air oven at 50°C. The percentage matrix swelling and erosion at time, t, were estimated from Eqs. 1 and 2, respectively.

$$\textit{Matrix swelling}\ (\%) = (W_s - W_i)/W_i \times 100. \quad (1)$$

$$\text{Matrix erosion}\ (\%) = (W_i - W_t)/W_i \times 100. \quad (2)$$

Where W_i is the initial starting weight of the matrix, W_s is the weight of the swollen matrix at time t, and W_t is the weight of matrix subjected to erosion for time, t. The data are the mean of three determinations.

Morphology of Swollen Tablets

The morphological changes occurring during hydration of the tablet was performed by placing tablet of the optimized formulation in excess distilled water in Petri dish. The tablets were taken out from the medium after hydration for 1, 5, and 12 h and were photographed by a digital camera (Sony, Japan).

In vivo Absorption Studies

Study design. The study was carried out to compare the pharmacokinetics of VenHCl from the prepared optimized PEO three-layer tablet formulation to a marketed extended release capsule. Following administration of single doses of 84.86 mg of VenHCl equivalent to 75 mg Venlafaxine, each using a two-treatment, two-period, randomized, crossover design.

Four healthy male volunteers participated in the study (weight 65 to 80 kg, age between 25 and 35 years, and height from 167 to 185 cm), and all are nonsmokers. The biochemical examination of the volunteers revealed normal kidney and liver function. The nature and the purpose of the study were fully explained to them. None of the volunteers were on drug treatment 1 week before the participation in the study. An

Table III. Composition of the Three-Layer Tablets and Their Observed Responses

Formula code	Factor			Type of hydrophilic polymer	Response		
	X_1	X_2	X_3		Y_1	Y_6	Y_{12}
1H	2	33	150	HPMC	29.82	57.97	100.00
2H	4	33	150		27.08	61.76	91.61
3H	2	66	150		24.34	49.75	78.66
4H	4	66	150		22.14	49.44	91.61
5H	2	33	240		28.27	43.28	86.24
6H	4	33	240		24.70	39.38	78.48
7H	2	66	240		18.85	39.80	58.12
8H	4	66	240		18.00	37.75	60.49
1P	2	33	150	PEO	23.38	76.19	100.00
2P	4	33	150		17.71	53.39	96.30
3P	2	66	150		23.02	39.01	73.50
4P	4	66	150		17.89	47.07	80.40
5P	2	33	240		18.73	42.01	75.60
6P	4	33	240		19.44	54.33	85.40
7P	2	66	240		18.73	38.38	61.20
8P	4	66	240		14.55	27.01	49.80

HPMC hydroxypropylmethylcellulose, PEO polyethyleneoxide

informed written consent was obtained from every volunteer. The study was approved by the Cairo University Protection of Human Subjects Committee and the protocol complies with the declarations of Helsinki and Tokyo for humans.

The study was performed on two periods. Period I, half the number of volunteers (group 1) received the optimized PEO three-layer tablet formulation (treatment A) and the other half (group 2) received the marketed extended release capsule (treatment B) which is considered as a reference standard. Both treatments were ingested with 150 ml of water after 12-h overnight fasting. Food and drinks were withheld for at least 2 h after dosing. A washout period of 1 week separated the periods. In period II, group 1 received treatment B and group 2 received treatment A.

The study was supervised by a physician who was also responsible for the volunteers' safety and collection of samples during the study. Blood samples (5 ml) were collected from the volunteers' forearm cubital vein using a hypodermic syringe through an indwelling cannula over a period of 24 h at the following sampling times: 0 min (pre-dose), 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, and 24 h after administration of each treatment. Plasma was separated by centrifugation at 2.000×*g* for 10 min. The plasma was pipetted into glass tubes and then frozen at −20°C until analysis by high-performance liquid chromatography (HPLC). The quantitative determination of VenHCl in human plasma was performed by a reverse-phase HPLC procedure described by Mandrioli *et al.* (16). The mobile phase was composed of a mixture of acetonitrile (25%, *v/v*) and a pH6.8, 40 mM phosphate buffer containing 0.25% (*v/v*) triethylamine (75%, *v/v*).

Pharmacokinetic analysis. Pharmacokinetic parameters for VenHCl, following oral administration of the two treatments, were determined from the plasma concentration time data by means of a model-independent method using a computer program, Kinetica® (version 5, Thermo Fischer Scientific). The terminal elimination rate constant K (h^{-1}) was obtained from the slope of the linear regression of the log-transformed plasma concentration–time data in the terminal phase. The $t_{1/2}$ (h) was calculated as 0.693/K. The maximum drug concentration (C_{max}, ng/ml) and the time to reach C_{max} (T_{max}, h) were obtained from the individual plasma concentration–time curves. The area under the curve AUC_{0-24} (ng h/ml) was determined as the area under the plasma concentration–time curve up to the last measured sampling time and calculated by the linear trapezoidal rule. The area under the curve from zero to infinity $AUC_{0-\infty}$ (ng h/ml) was calculated as $AUC_{0-\infty} = AUC_{0--24} + C_t/K$ where C_t is the last measured concentration at the time *t*.

Statistical analysis. All the results were expressed as mean ± standard deviation (SD). The pharmacokinetic parameters, C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ were compared between treatments A and B with the ANOVA test for the untransformed data and calculating 90% confidence interval of the ratio of test/reference using log-transformed data. The inclusion of the confidence interval within 0.8–1.25 was taken as a demonstration of bioequivalence (17). The nonparametric Signed Rank Test (Mann–Whitney's test) was used to compare the medians of t_{max} for treatments A and B using the software Minitab®. The untransformed values for $t_{1/2}$ was compared with ANOVA test. The level of significance was α=0.05. A *p* value of ≤0.05 was considered statistically significant. The sample size (n=4) was selected not based on statistical consideration but rather on economic consideration.

RESULTS AND DISCUSSION

The aim of this work was to develop new matrix systems of VenHCl, a highly water soluble drug, to provide zero-order controlled release for once-daily administration. An ideal drug release profile (i.e., 20% in the first hour and a constant drug release thereafter) was considered as a target release profile. Drug release from a matrix tablet involves liquid penetration into the dosage form followed by dissolution of the drug and finally its diffusion.

Drug–Excipients Compatibility Studies

DSC has been proposed to be a rapid method for evaluating physicochemical interactions between components of the formulation through the comparison of thermal curves of pure substances with the curve obtained from a 1:1 physical mixture and, therefore, select adequate excipients with suitable compatibility (18). The DSC thermogram of the drug gave a sharp melting endotherm at 212.87°C. The DSC thermograms of Compritol® and Precirol® show characteristic endothermic peaks at 71.99°C and 56.25°C, respectively, corresponding to their melting point. There was no shift in the endotherms of venHCl,

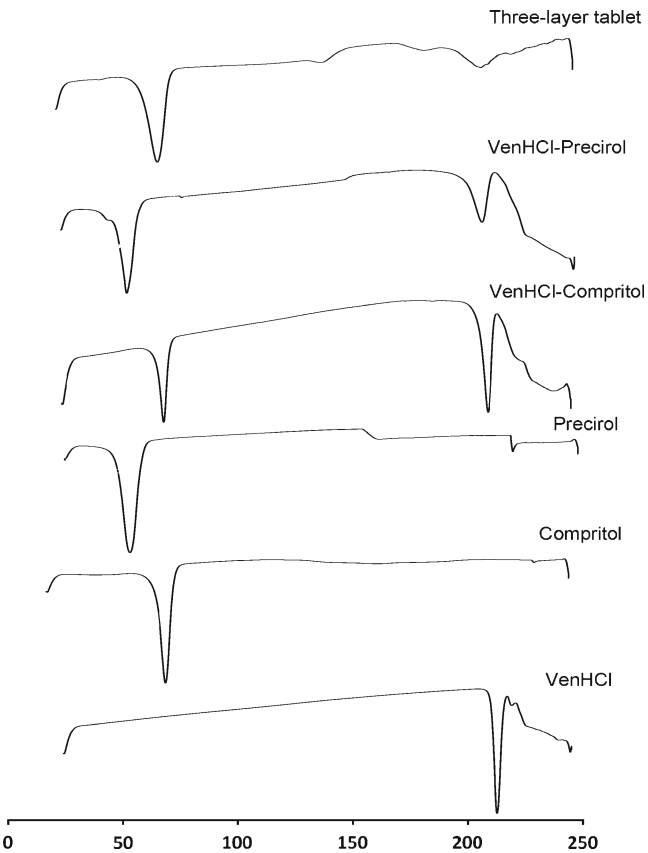

Fig. 1. DSC thermograms of venlafaxine hydrochloride and excipients

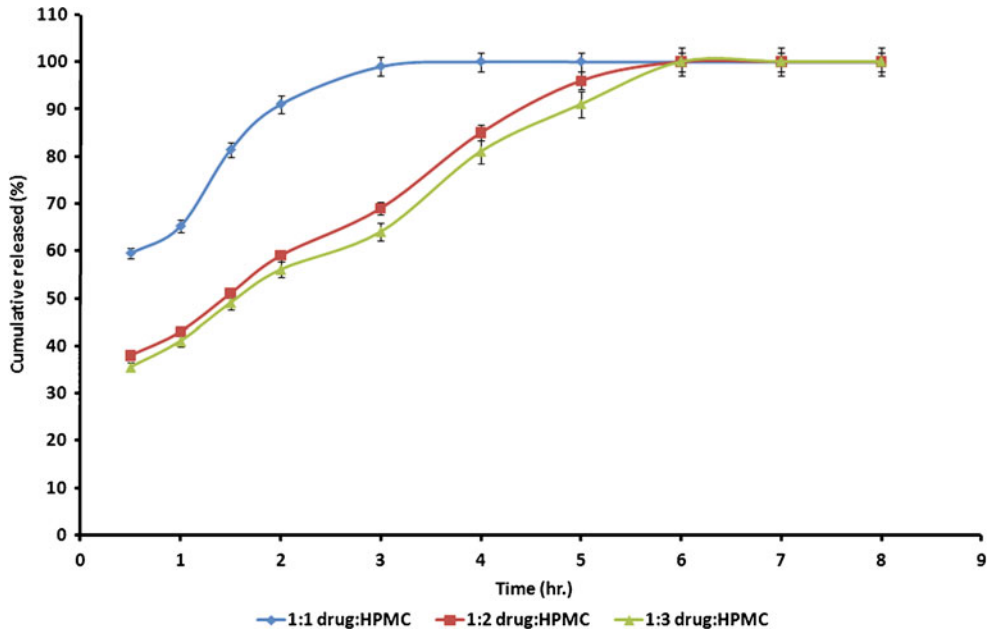

Fig. 2. *In vitro* release of VenHCl from HPMC-based matrix tablets

Compritol® and Precirol® in the drug–excipient mixtures indicating compatibility of the drug with all the excipients. The DSC curve of three-layer tablet shows the characteristic endothermic peaks of drug and Compritol® and an endothermic peak at 138.08°C corresponding to dehydration of lactose monohydrate. The comparative DSC thermograms of the VenHCl, individual excipients and drug–excipient mixtures are depicted in Fig. 1.

In vitro Release of VenHCl from HPMC-Based Hydrophilic Matrix Tablet

Figure 2 shows the *in vitro* release of VenHCl from HPMC-based hydrophilic matrix tablet. It is obvious that all formulations displayed complete drug release and increasing the ratio of HPMC from 1:1 to 1:4 delayed the time required for complete release of drug from 3 to 5 h. The retardant effect of HPMC remarkably increases with raising drug–polymer ratio up to 1:2. However, a further increase of HPMC ratio resulted in a slight retardation of drug release. This slow release was due to the formation of a thick gel structure that delayed drug release from the tablet matrix, where hydration of the HPMC particles resulted in extensive swelling (19). A thick gel layer result in a considerable increase in the diffusion pathway for the drug molecules, and consequently, the drug release rate was reduced. The *in vitro* release profiles of all HPMC formulations are characterized by burst release (>35% after 1 h). This could be attributed to the dissolution of the drug mainly located on the surface of the matrix and the delayed gel layer formation. In the initial

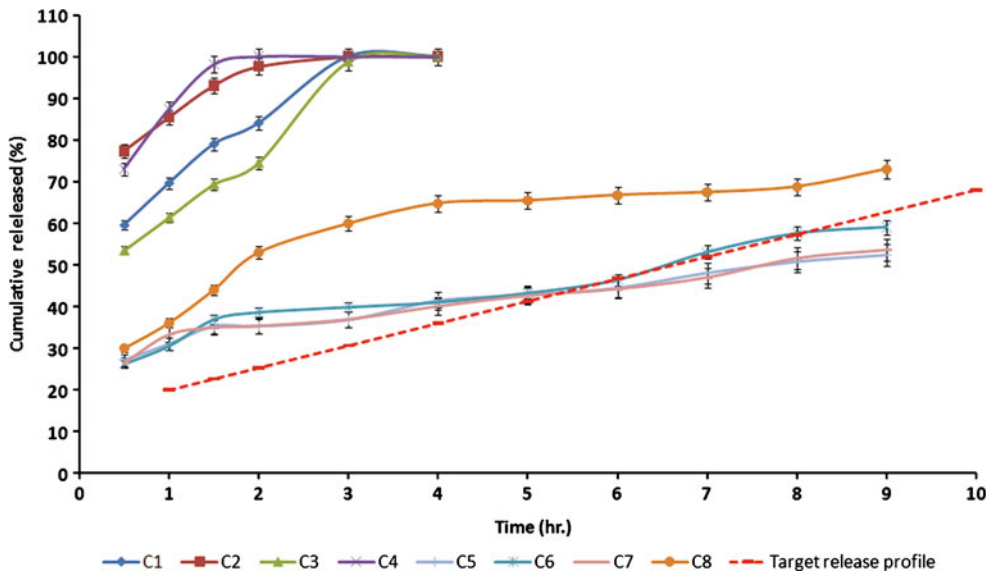

Fig. 3. *In vitro* release of VenHCl from wax-based matrix tablets

dissolution stages, the gel layer starts to form with small thickness resulting in a limited diffusion pathway for the drug molecules to diffuse out. As the time passes, the gel thickness increases leading to retardation of liquid penetration and the subsequent drug release (7).

In vitro Release of VenHCl from Wax-Based Matrix Tablet

To study the effects of wax levels, the amount of drug in the formulated tablets was held constant at 84.86 mg, while the wax level varied and keeping the total tablet weight equal to 250 mg using lactose. Figure 3 shows the *in vitro* release of VenHCl from matrices made from the physical mixtures or solid dispersions of Compritol® or Precirol®.

The drug release was higher from the matrices prepared with physical mixtures than from tablets with solid dispersions. Precirol®-based physical mixtures of VenHCl exhibited the highest drug release followed by Compritol®-based physical mixtures, Compritol®-based solid dispersion, and finally Precirol®-based solid dispersion. The slower release from the solid dispersion matrices is due to almost complete coating of the drug particles by the wax melted in the process of fusion. Thus, the penetration of the dissolution medium into the matrix will be low compared with matrices prepared by physical mixtures and, hence, the dissolution and release of the drug occurs at a slower rate (20). It is obvious that increasing the ratio of wax in the matrices resulted in a remarkable decrease in the drug release rate. This may be mainly due to the negative effect of the hydrophobic matrix against the penetration of the aqueous dissolution medium and partially due to the reduction of the amount of lactose in the matrix. Lactose could produce pores and channels in the matrix due to its high solubility in water resulting in higher drug dissolution rate (21).

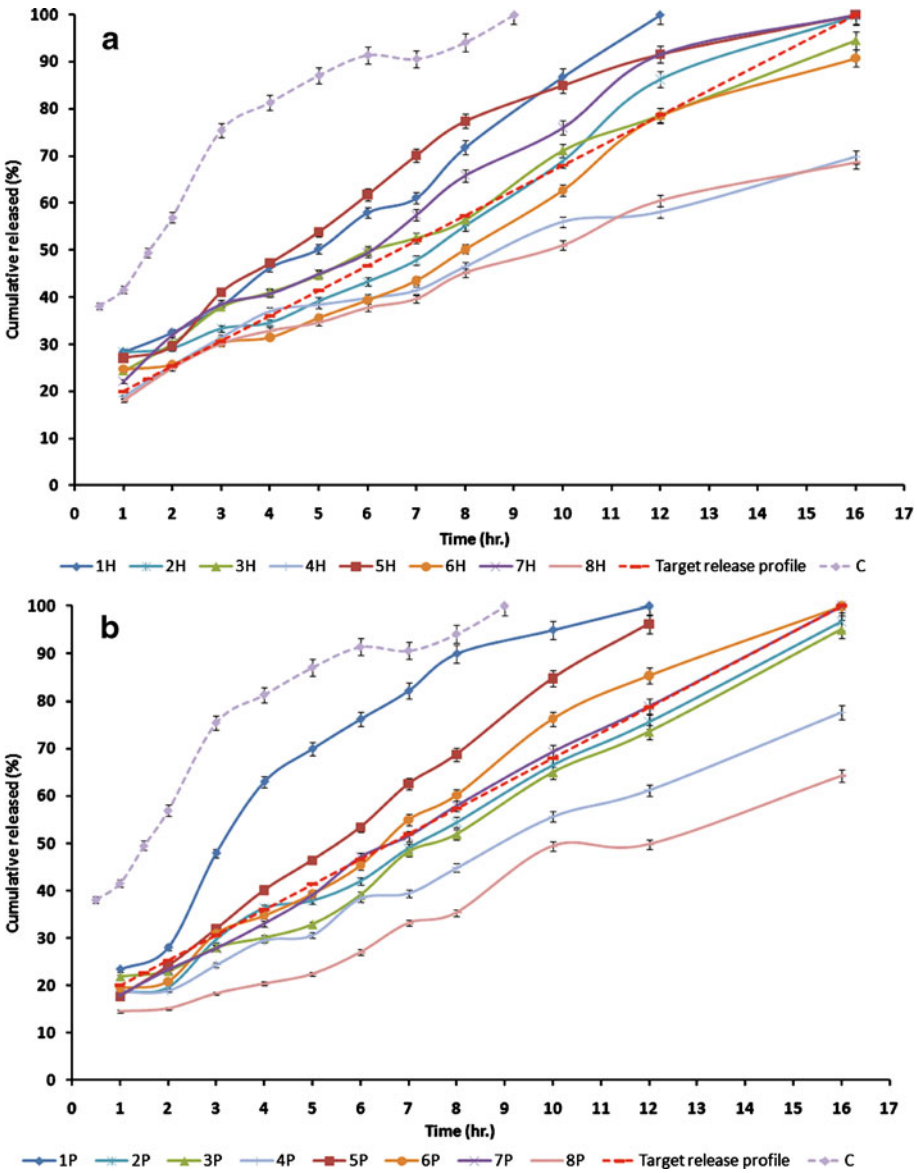

Fig. 4. *In vitro* release of VenHCl from three-layer tablets. **a** HPMC three-layer tablets, **b** PEO three-layer tablets

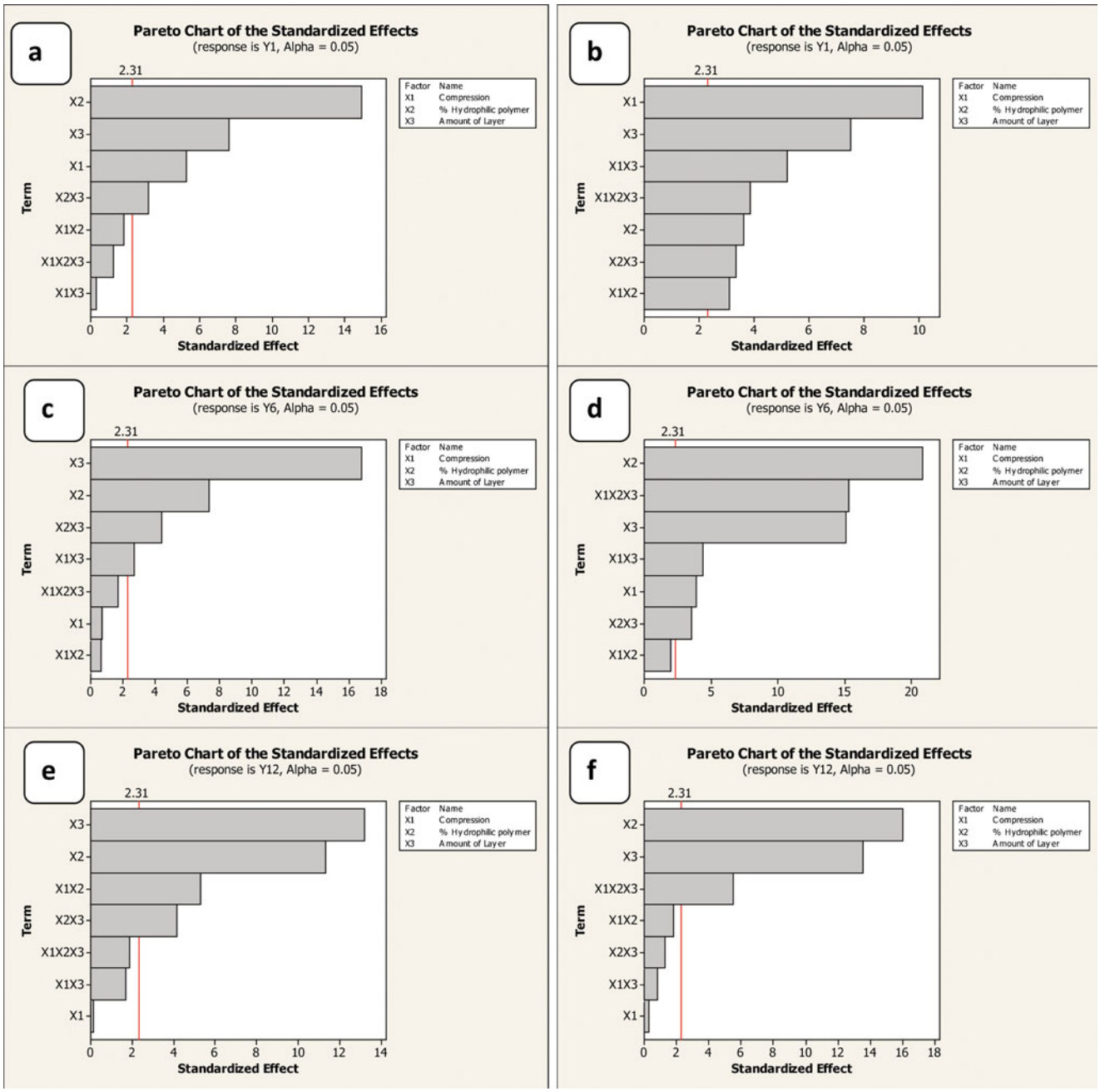

Fig. 5. Standardized Pareto charts for Y_1, Y_6, and Y_{12} (**a**, **c,** and **e** for HPMC three-layer tablet; **b**, **d,** and **f** for PEO three-layer tablet)

Visual inspection of the appearance of the tablets, at the end of the dissolution test, revealed that all wax-based tablets remained intact without any significant change in their shape indicating that the water soluble drug diffused across the waxy matrix. It is worthy to note that wax-based matrix tablets containing high levels of Precirol® exhibited bad compressibility as indicated by peeling of the prepared tablets under the effect of punch pressure.

Table IV. Polynomial Equations for the Quantitative Effect of Independent Variables (X_1, X_2, X_3) on the Responses (Y_1, Y_6, Y_{12})

Type of hydrophilic polymer	Equation
HPMC	$Y_1 = 23.546 - 1.141\ X_1 - 3.235\ X_2 - 1.653\ X_3 + 0.397\ X_1X_2 + 0.063\ X_1X_3 - 0.695\ X_2X_3 + 0.266\ X_1X_2X_3$
	$Y_6 = 46.206 - 0.301\ X_1 - 3.126\ X_2 - 7.155\ X_3 - 0.274\ X_1X_2 - 1.149\ X_1X_3 + 1.881\ X_2X_3 + 0.725\ X_1X_2X_3$
	$Y_{12} = 78.635 - 0.101\ X_1 - 8.22\ X_2 - 9.573\ X_3 + 3.835\ X_1X_2 - 1.213\ X_1X_3 - 3.019\ X_2X_3 - 1.366\ X_1X_2X_3$
PEO	$Y_1 = 18.702 - 1.739\ X_1 - 0.618\ X_2 - 1.286\ X_3 - 0.530\ X_1X_2 + 0.893\ X_1X_3 - 0.574\ X_2X_3 - 0.662\ X_1X_2X_3$
	$Y_6 = 45.994 - 1.681\ X_1 - 9.074\ X_2 - 6.573\ X_3 + 0.874\ X_1X_2 + 1.912\ X_1X_3 + 1.53\ X_2X_3 - 6.648\ X_1X_2X_3$
	$Y_{12} = 75.83 - 0.2\ X_1 - 11.26\ X_2 - 9.53\ X_3 - 1.29\ X_1X_2 - 0.59\ X_1X_3 - 0.93\ X_2X_3 - 3.88\ X_1X_2X_3$

HPMC hydroxypropylmethylcellulose, PEO polyethyleneoxide

Table V. Predicted and Observed Responses of the Optimized Polyethyleneoxide Formulation

Response	Predicted	Observed	Residual[a]
Y_1	19.99	16.23	3.76
Y_2	46.73	49.69	−2.96
Y_3	78.66	81.45	−2.79

[a] Residual: predicted value − observed value

The *in vitro* release profiles of wax-based matrix tablet are characterized by burst release and were found to fit Higuchi diffusion model (data are not shown).

In vitro Release of VenHCl from Three-Layered Matrix Tablets

Based on the above results, we decided to prepare three-layer controlled release tablets of VenHCl that approach zero-order kinetics for once-daily administration and prevent the burst release. The top and bottom hydrophilic barrier layers composed of HPMC or PEO that was dry mixed with lactose and a middle wax based matrix composed of VenHCl solid dispersion of Compritol®. The bad compressibility of wax-based matrices containing high content of wax (1:1.75) especially Precirol® and the high drug release observed from the wax-based matrices containing low content of wax (1:1) encouraged us for the preparation of wax-based matrix tablet containing solid dispersion of VenHCl and Compritol® in a ratio 1:1.25 (formulation C). As shown in Fig. 4, the *in vitro* release profile of formulation C is characterized by a high burst release (>38% after 30 min) and complete release of the drug after 9 h. In this system, drug release occurred from all three dimensions of the matrix device via Higuchi diffusion. The nonlinear release is a result of decreasing rate of drug release with time.

One of the benefits of using the three-layer tablet was to reduce dose dumping for high solubility drug substances. The compression with polymeric layers on both sides of tablet could prolong and modify drug release to achieve constant release rate. In this system, the initial release of the drug from the middle matrix layer was effectively slowed by delaying and/or preventing drug diffusion from the two faces of the middle layer. The early release of drug occurred from the greatly reduced surface along the peripheral wall. However, the decreasing release rate from the middle layer can be compensated for by the delayed diffusion from the two coated faces as a result of polymer hydration/dissolution at later time, leading to an apparent linear release (22). As shown in Fig. 4, the drug release rate from three-layer tablet, containing HPMC and PEO as hydrophilic barriers was obviously lower than that single layer matrix tablet (formulation C).

Increasing amount of hydrophilic barrier layers and the percent of hydrophilic polymers in these layers apparently retarded the drug release as shown in Fig. 4. Formulations 4 and 8 of HPMC and PEO based three-layer tablets, containing the highest content of hydrophilic polymer (66%), showed the slowest release rates. However, formulations containing the lowest percent of hydrophilic polymers and compressed at a compression force of 2 tons showed the most rapid release rate as indicated by formulation 1 and 5 of HPMC and PEO based three-layer tablets. It is worthy to note that in all the formulations, the middle layer and barrier layers maintained their integrity in the three-layer tablets during the release study.

Analysis of Factorial Design

A two-level experimental design provides sufficient data to fit a polynomial equation, which is in the following form:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}(X_1X_2) + b_{13}(X_1X_3) + b_{23}(X_2X_3) + b_{123}(X_1X_2X_3) \quad (3)$$

Where Y is the dependent variable; b_0 is the intercept; and b_1–b_{123} are the coefficients for the factors X_1, X_2, and X_3 and their interaction terms (23). The standardized effect of

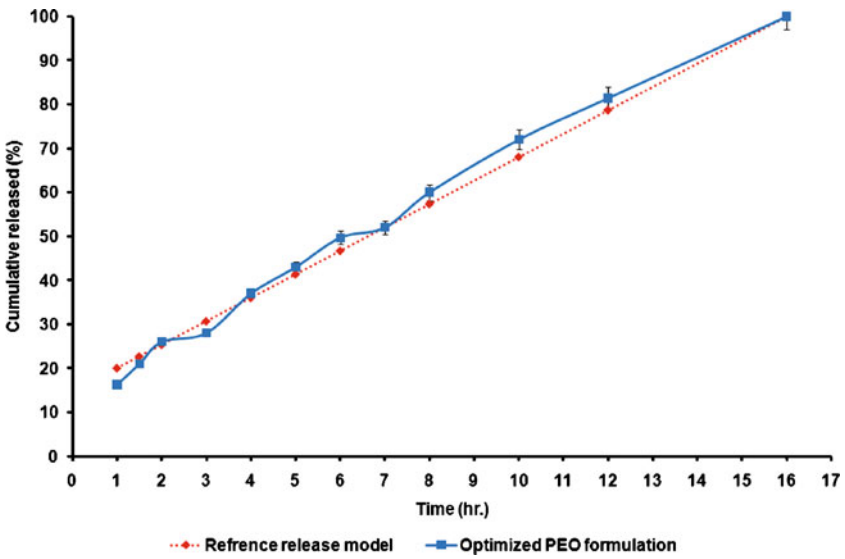

Fig. 6. *In vitro* release of VenHCl from the optimized PEO three-layer tablet and the reference release model

Table VI. Kinetic Analysis of the *In vitro* Release Data of VenHCL

	Zero			Diffusion			Peppas			
Formulation code	R^2	Slope	Intercept	R^2	Slope	Intercept	R^2	N	K	The fitted model
1H	0.9928	6.61	18.96	0.9586	29.30	−9.89	0.9480	0.447	25.51	Zero
2H	0.9444	5.18	16.56	0.8495	22.30	−4.55	0.8300	0.369	23.83	Zero
3H	0.9898	4.80	20.81	0.9642	21.53	−0.71	0.9740	0.439	23.05	Zero
4H	0.9611	3.43	19.40	0.9761	15.70	3.29	0.9840	0.457	18.59	Peppas
5H	0.9765	6.33	21.77	0.9817	28.82	−7.61	0.9490	0.532	23.68	Diffusion
6H	0.9512	4.78	14.47	0.8613	20.68	−5.20	0.8550	0.388	20.93	Zero
7H	0.9877	5.97	17.28	0.9592	26.55	−9.00	0.9740	0.481	22.08	Zero
8H	0.9830	3.51	17.10	0.9669	15.81	1.21	0.9780	0.468	17.38	Zero
1P	0.8980	7.25	25.52	0.9762	34.10	−10.64	0.9530	0.714	21.26	Diffusion
2P	0.9907	5.30	12.22	0.9612	23.72	−11.42	0.9510	0.596	15.62	Zero
3P	0.9766	4.99	12.36	0.9106	21.90	−8.90	0.8820	0.516	17.19	Zero
4P	0.9879	4.11	12.32	0.9470	18.28	−5.75	0.9320	0.550	14.57	Zero
5P	0.9987	7.30	10.25	0.9742	32.76	−22.52	0.9860	0.668	16.25	Zero
6P	0.9912	6.31	10.17	0.9488	28.03	−17.52	0.9380	0.611	16.11	Zero
7P	0.9978	5.70	11.51	0.9647	25.51	−13.92	0.9680	0.599	15.84	Zero
8P	0.9579	3.64	7.46	0.8954	15.98	−8.08	0.8970	0.586	10.73	Zero
C	0.9630	11.82	32.73	0.9717	35.62	8.96	0.9510	0.398	45.39	Diffusion

the independent variables and their interaction on the dependent variable was investigated by preparing Pareto charts (Fig. 5). These charts consist of bars, the lengths of which are proportional to the absolute value of the estimated effects, divided by the standard error. These were utilized to show the effect (in decreasing order of importance) of the independent variables and their interactions on the dependant variables. The chart includes a vertical reference line at the critical p value of 0.05. An effect that exceeds the vertical line is considered to be statistically significant (24, 25).

The fact that the bars for the variables X_2 and X_3 extend after the reference line and the relatively larger coefficient for these terms in the polynomial equations for Y_1, Y_6, and Y_{12} (Table IV) indicate that percentage of hydrophilic polymer in the hydrophilic layer and amount of hydrophilic layer are significant in controlling the release of VenHCl throughout the dissolution time for both PEO and HPMC polymers. The negative coefficients of both independent variable X_2 and X_3 indicate that they have a retardant effect on VenHCl release through formation of a thick gel layer as previously mentioned.

The bar for the variable X_1 appears before the reference line in the Pareto chart for Y_{12} (Fig. 5e, f) indicating that the compression force is only important in controlling VenHCl release during the early stage of drug release, which was confirmed by the relatively large coefficient for X_1 in the polynomial equation for Y_1 (Table IV). The negative coefficient of the independent variable X_1 indicates that it has a retardant effect on VenHCl release. It could be assumed that the variation in compression forces should be closely related to a change in the porosity of tablets. Thus, tablets made at lower compression force show faster initial drug release due to rapid liquid penetration. Once the hydrophilic layer become hydrated and swollen, the porosity of the hydrated matrix is independent of the initial porosity, consequently the compression force become to have little influence on drug release (26).

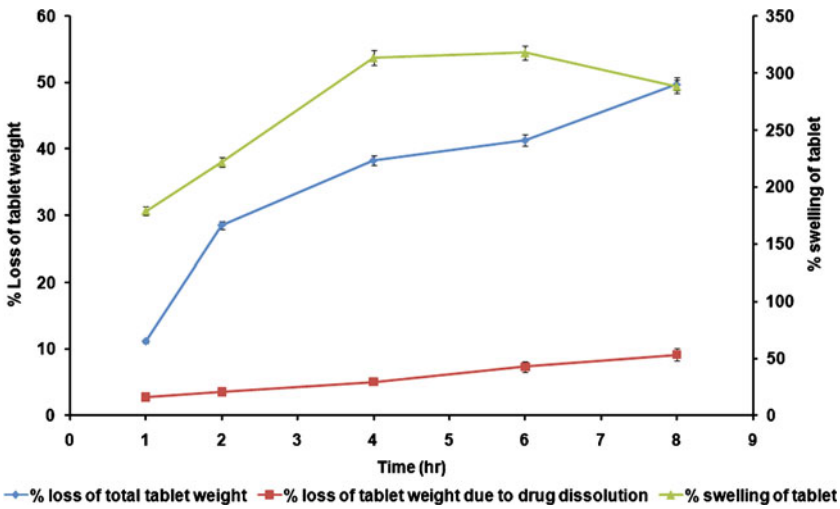

Fig. 7. The swelling and the loss of tablet weight due to erosion of the optimized PEO three-layer tablet in distilled water at 37°C

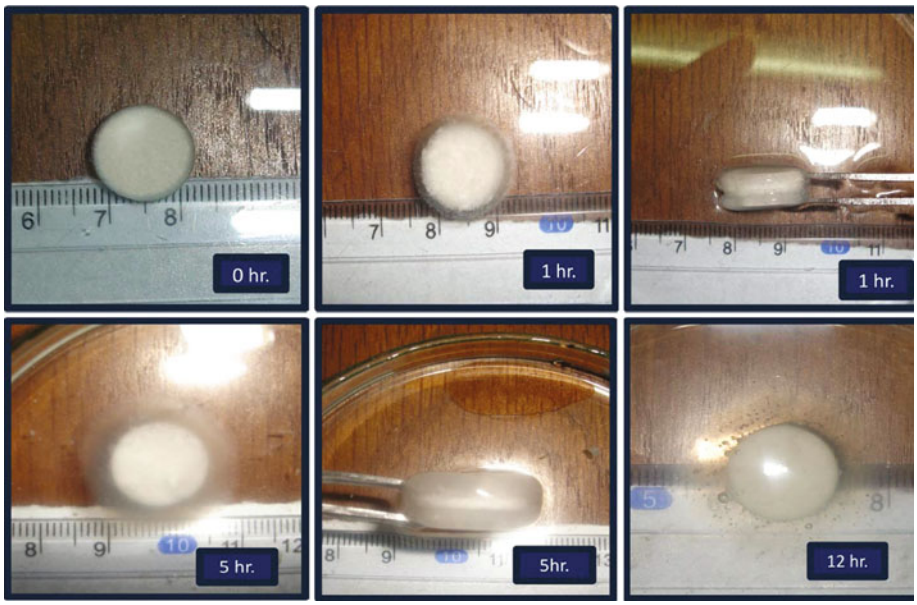

Fig. 8. Photoimages of the optimized PEO three-layer tablet after hydration in distilled water at different time intervals: 0 h (top view), 1 h (top and side view), 5 h (top and side view), and 12 h (top view)

Optimization

In order to find the level of each independent variable that will lead to an optimized formulation, the optimization process was performed for X_1, X_2, and X_3 using the following target ranges: $18\% \leq Y_1 \leq 22\%$; $42\% \leq Y_6 \leq 51\%$; and $71\% \leq Y_{12} \leq 86\%$. The target ranges of these responses were determined based on the target release model deduced form the VenHCl release profile of a marketed extended release capsule of VenHCl.

The optimization process was performed using Minitab® software. The optimized levels of each independent variable were based on the criterion of desirability. The optimized levels of compression force (X_1), percentage of hydrophilic polymer (X_2), and amount of hydrophilic layer (X_3) of HPMC three-layer tablets are 3.887 tons, 66%, and 180 mg, respectively, with a composite desirability of 0.7585.

The optimized levels of X_1, X_2, and X_3 of PEO three-layer tablets are 2.87 tons, 57%, and 158 mg, respectively, with a composite desirability of 0.995 which is closer to 1

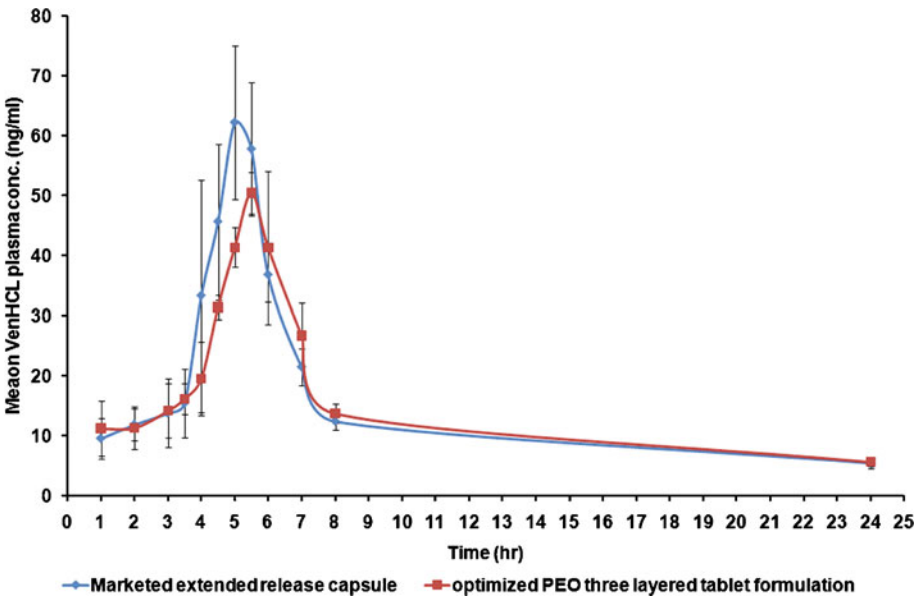

Fig. 9. Mean (±SD) plasma VenHCl concentrations following administration of 75 mg venlafaxine in optimized PEO three-layer tablet and marketed extended release capsule (reference) in four subjects

compared to that of HPMC optimized formulation, indicating that PEO-optimized formulation is more successful in achieving the desired release profile.

Table V shows the predicted and observed responses for the optimized PEO formulation, indicating that the release profile of the VenHCl from the optimized PEO formulation was close to the predicted values. The dissolution profiles of the optimized PEO formulation and the reference release model are presented in Fig. 6. These dissolution profiles were compared using two fit factors, difference factor (f_1) and similarity factor (f_2) (27). The calculated values of f_1 and f_2 were 4.131 and 79.356, respectively, indicating that the dissolution profile of the optimized PEO formulation is similar to that of the reference release model.

Kinetic Analysis of Release Data

The estimated parameters from curve fitting to power law, Higuchi and zero order equations are shown in Table VI. All formulations release profile was fitting to zero order kinetics (large R^2) except formulations 5H and 1P which fitted Higuchi diffusion model and 4H which fitted Korsemeyer–Peppas model. These results suggested that nearly all the developed three-layer tablets showed zero-order release. Total drug release involves both diffusion of drug molecules from the lateral surface of the core tablet and delayed diffusion through the swollen top and bottom barrier layers as well as erosion of the formed gel over time.

Swelling and Erosion Studies

The optimized PEO three-layer tablet was subjected to swelling and erosion studies to determine the effect of the hydrophilic barrier swelling and the subsequent erosion in the late state of the dissolution on the release of the drug. The swelling and the loss of weight of the optimized PEO three-layer tablet are shown in Fig. 7. It is obvious that the tablets underwent rapid swelling (179% in 1 h) and reached their maximum swelling value (313%) between 4 and 6 h followed by reduction of the percentage of swelling. However, the initial erosion of the tablets was rapid (28.5% in 2 h) followed by a constant erosion rate (3.32%/h). Figure 7 also reveals that the loss of total tablet weight is mainly due to PEO erosion/dissolution and that the drug dissolution/diffusion has a little effect on the loss of tablet weight. These observations emphasized that the decreasing release rate at late state from the lateral surface of the middle layer was balanced not only by the delayed diffusion of the drug through the swollen hydrophilic barriers but also through the dissolution and erosion of these barrier layers resulting in zero-order release. This conclusion could be further confirmed by photo images shown in Fig. 8 of the optimized PEO three-layer tablet before and after hydration at different time intervals. It is clear that a gel layer was formed around the tablet after hydration, and the dimension of tablet was increased with time. Finally, a remarkable dissolution of the hydrophilic barriers was observed.

In vivo Absorption Studies

Figure 9 shows the mean VenHCl plasma concentration *vs*. time profiles obtained after single oral administrations of both the optimized PEO three-layer tablet formulation and the marketed extended release capsule. The mean pharmacokinetic characteristics are summarized in Table VII. Statistically insignificant differences ($p>0.05$) were found between the pharmacokinetic parameters AUC_{0-24}, $AUC_{0-\infty}$, T_{max}, and $t_{1/2}$ determined for both the optimized PEO three-layer tablet and the marketed extended release capsule. The 90% confidence intervals for the test/reference mean ratio of the log-transformed data of AUC_{0-24} and $AUC_{0-\infty}$ are (0.939–1.030) and (0.811–1.107), respectively. The 90% confidence interval for AUC_{0-24} and $AUC_{0-\infty}$ are within (0.8–1.25), which satisfied the bioequivalence criteria. The mean C_{max} estimated from the optimized PEO three-layer tablet (53.19 ng/ml) was smaller and statistically significantly different ($p=0.0196$) relative to the mean from the marketed extended release capsule (67.78 ng/ml) and the 90% confidence interval (0.616–1.001) failed to satisfy the bioequivalence criteria, although the *in vitro* VenHCl release profile of the optimized PEO three-layer tablet was similar to the target release profile. This result could be attributed to the small number of subjects and/or the difference between the two dosage forms used. The marketed extended release capsule is formed from pellets whose stomach residence time is less affected by the gastric emptying rate.

Based on these findings, it could be concluded that a promising once-daily extended-release three-layer tablet of the highly water soluble drug, VenHCl, was successfully designed. However, because of the small number of subjects recruited in the study, the results can only be considered preliminary, and further studies with a larger number of subjects should be conducted to prove the clinical usability of the experimental extended-release formulation.

Table VII. The Mean (± SD) for Pharmacokinetic Parameters of VenHCL After Oral Administration of Optimized PEO Three-Layer Tablet Formulation and the Marketed Extended Release Capsule to Four Healthy Human Volunteers Under Fasted Condition

Parameter	Optimized PEO three-layered tablet formulation	Marketed extended release capsule	Statistical test (p)
C_{max} (ng/ml)	53.19±5.30	67.78±7.57	0.0196
T_{max} (h)[a]	5.5±0.25	5.25±0.29	0.1939
AUC_{0-24} (ng h/ml)	326.43±13.75	332.20±23.16	0.6832
$AUC_{0-\infty}$ (ng h/ml)	392.18±23.52	414.91±43.80	0.3957
$t_{1/2}$ (h)	8.44±1.25	10.49±1.87	0.1186

[a] Median
PEO Polyethyleneoxide

CONCLUSION

The three-layer tablet formulations demonstrated sustained drug release and lower burst release compared to both hydrophilic and wax-based matrices. The release profiles of the optimized PEO three-layer tablet, composed of 158 mg hydrophilic barrier layers containing 57% PEO, was comparable to that of the target release model deduced form the dissolution profile of a marketed extended release capsule of VenHCl. The *in vivo* study suggests that optimized PEO three-layer formulation developed in this work may be comparable to the marketed VenHCl capsule in the form-coated pellets that are reported to suffer from low productivity, long processing time, and high cost.

REFERENCES

1. de Oliveira RA, Cunha GM, Borges KD, de Bruin GS, dos Santos-Filho EA, Viana GS, *et al*. The effect of venlafaxine on behaviour, body weight and striatal monoamine levels on sleep-deprived female rats. Pharmacol Biochem Behav. 2004;79:499–506.
2. Gohel MC, Soni CD, Nagori SA, Sarvaiya KG. Modulation of venlafaxine hydrochloride release from press coated tablet. Indian J Pharm Sci. 2008;70:292–7.
3. Gohel MC, Bariya SH. Fabrication of triple-layer matrix tablets of venlafaxine hydrochloride using xanthan gum. AAPS PharmSciTech. 2009;10:624–30.
4. Makhija SN, Vavia PR. Once daily sustained release tablets of venlafaxine, a novel antidepressant. Eur J Pharm Biopharm. 2002;54:9–15.
5. Abdul S, Poddar SS. A flexible technology for modified release of drugs: multi layered tablets. J Control Release. 2004;97:393–405.
6. Chidambaram N, Porter W, Flood K, Qiu Y. Formulation and characterization of new layered diffusional matrices for zero-order sustained release. J Control Release. 1998;52:149–58.
7. Efentakis M, Peponaki C. Formulation study and evaluation of matrix and three-layer tablet sustained drug delivery systems based on Carbopols with isosorbite mononitrate. AAPS Pharm SciTech. 2008;9:917–23.
8. Conte A, Maggi L, Colombo P, la Manna A. Multi-layered hydrophilic matrices as constant release devices (Geomatrix™ Systems). J Control Release. 1993;26:39–47.
9. The United States Pharmacopeia 30/The National Formulary 25. Rockville: USP Convention; 2006.
10. Wagner JG. Interpretation of percent dissolved-time plots derived from *in vitro* testing of conventional tablets and capsules. J Pharm Sci. 1969;58:1253–7.
11. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharm Sci. 1961;50:874–5.
12. Higuchi T. Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145–9.
13. Korsemeyer RW, Gurnya R, Doelkera E, Buria P, Peppas NA. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25–35.
14. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985;60:110–1.
15. Sinha Roy D, Rohera BD. Comparative evaluation of rate of hydration and matrix erosion of HEC and HPC and study of drug release from their matrices. Eur J Pharm Sci. 2002;16:193–9.
16. Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. Analysis of the second generation antidepressant venlafaxine and its main active metabolite O-desmethylvenlafaxine in human plasma by HPLC with spectrofluorimetric detection. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;856:88–94.
17. Mahaguna V, Talbert RL, Peters JI, Adams S, Reynolds TD, Lam FY, *et al*. Influence of hydroxypropylmethylcellulose polymer on *in vitro* and *in vivo* performance of controlled release tablets containing alprazolam. Eur J Pharm Biopharm. 2003;56:461–8.
18. Bernardi LS, Oliveira PR, Murakami FS, Silva MAS, Borgmann SHM, Cardoso SG. Characterization of venlafaxine hydrochloride and compatibility studies with pharmaceutical excipients. J Therm Anal Cal. 2009;97:729–33.
19. Phaechamud T. Variables influencing drug release from layered matrix system comprising hydroxypropylmethylcellulose. AAPS PharmSciTech. 2008;9:668–74.
20. Li FQ, Hu JH, Deng JX, Su H, Xu S, Liu JY. *In vitro* controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets. Int J Pharm. 2006;324:152–7.
21. Liu J, Zhang F, McGinity JW. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. Eur J Pharm Biopharm. 2001;52:181–90.
22. Qiu Y, Chidambaram N, Flood K. Design and evaluation of layered diffusional matrices for zero-order sustained-release. J Control Release. 1998;51:123–30.
23. Singh J, Philip AK, Pathak K. Optimization studies on design and evaluation of orodispersible pediatric formulation of indomethacin. AAPS PharmSciTech. 2008;9:60–6.
24. Rekhi GS, Nellore RV, Hussain AS, Tillman LG, Malinowski HJ, Augsburger LL. Identification of critical formulation and processing variables for metoprolol tartrate extended-release (ER) matrix tablets. J Control Release. 1999;59:327–42.
25. Solanki AB, Parikh JR, Parikh RH. Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level Box-Behnken design. AAPS PharmSciTech. 2007;8:E86.
26. Velasco MV, Ford JL, Rowe P, Rajabi-Siahboomi AR. Influence of drug:hydroxypropylmethylcellulose ratio, drug and polymer particle size and compression force on the release of diclofenac sodium from HPMC tablets. J Control Release. 1999;57:75–85.
27. FDA Center for Drug Evaluation and Research. Guidance for industry: dissolution testing of immediate release solid oral dosage form. Rockville: FDA; 1997.