ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 8, Issue 3, 2015

ISSN - 0974-2441

Research Article

DESIGN AND *IN-VITRO* EVALUATION OF CONTROLLED RELEASE TRI-LAYER VENLAFAXINE HYDROCHLORIDE TRANSDERMAL PATCH

SAFOORA AFREEN[1], VAMSHI VISHNU Y[1], SUHAIR S AL SALEH[3], SYED WAJID[2]*, SHIVA KUMAR R[1], MOHAMED N AL-ARIFI[2], SUHA S ALSALEH[4]

[1]Department of Pharmaceutics, Vikas College of Pharmacy, Jangaon, Warangal - 506 167, Telangana, India. [2]Department of Clinical Pharmacy, Drug and Poison Information Center, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia. [3]Ministry of Health, Riyadh, Kingdom of Saudi Arabia. [4]Department of Family Medicine, Imam Abdulrahman bin Faisal Hospital, Dammam-National Guard Health Affairs, Dammam, Kingdom of Saudi Arabia. Email: wali@ksu.edu.sa

Received: 09 March 2015, Revised and Accepted: 30 March 2015

ABSTRACT

Objectives: The purpose of this study was to design a suitable transdermal therapeutic system for venlafaxine hydrochloride (VFH) with the objective to prolong the release to be used for controlled release drug delivery.

Methods: Transdermal patches of VFH with a hydroxypropyl methylcellulose drug reservoir were prepared by the solvent evaporation technique. In this investigation, the Eudragit RSPO membrane in different concentrations was cast to achieve controlled release of the drug. The absence of physiochemical interactions between VFH and the polymers was confirmed by Fourier transform infrared spectroscopy. The physicochemical parameters and *in-vitro* drug release studies of formulations were performed and data of optimized formulation were fitted to various kinetic models.

Results: The results indicated that suitable tri-layered transdermal patches of VFH with controlled drug release could be prepared. All the formulations exhibited satisfactory physicochemical characteristics. Among the formulations prepared, formulation F2 showed optimized controlled release for 24 hrs (96.42%) with the flux of 28.28 μg/cm^2/hr and permeability coefficient of 1.1315×10^{-3} cm/hr. Drug release from optimized patch followed Korsmeyer-Peppas model and was mediated by Fickian diffusion mechanism.

Conclusion: Hence, the development of adhesive type tri-layered transdermal patches for VFH might be a promising one to control the drug release for 24 hrs with reduced side-effects.

Keywords: Venlafaxine hydrochloride, Tri-layered transdermal patch, Plasticizer, *In-vitro* drug release study, *In-vitro* permeation study.

INTRODUCTION

Discovering a new medicine is a very expensive and time-consuming process. However, re-designing the modules and means to transport medicine into the body is a less demanding and more lucrative task [1]. Transdermal delivery provides a leading edge over oral and parenteral routes by increasing patient compliance and avoiding first pass metabolism, respectively. In transdermal drug delivery system, transdermal patch is a medicated adhesive patch that is placed on the skin to deliver drug through the skin and to the systemic circulation at a predetermined rate over a prolonged period of time [2].

Depression makes a person feel sad, hopeless, worthless, pessimistic, and guilty. Depression must be taken seriously because of the high rate of suicide associated with it. Venlafaxine hydrochloride (VFH), a novel antidepressant [3] has been selected as a model drug because it exhibits required pharmacokinetic and physicochemical properties for controlled transdermal delivery system. It is a selective serotonin and norepinephrine reuptake inhibitor used widely for the treatment of depression and generalized anxiety disorder. It has low molecular weight (313.9), poor bioavailability (45%), short biological half-life (5 hrs), and lipophilic nature (log P, 2.74); need for long-term treatment and repetitive dosing so as to maintain adequate plasma levels of drug [4]. Its water solubility is 572 mg/ml which is very high and may cause burst effect by getting in to the solution very quickly [5]. Moreover, oral use of VFH is associated with a number of predictable adverse effects such as nausea, headache, insomnia, dizziness, sweating, and dry mouth [6]. These qualities make this drug an interesting candidate for transdermal administration.

As the drug belongs to BCS Class I, it is necessary to retard dissolution to ensure extended release of the drug. Thus, by considering its short half-life and to minimize the number of doses, thereby increasing the patient compliance, this study has been undertaken with an aim to prolong the release of VFH by incorporating it into the transdermal therapeutic system to be used for controlled release drug delivery.

METHODS

Materials

VFH was obtained from R.K. Chemicals Ltd.; hydroxypropyl methylcellulose (HPMC) E50cps and Eudragit RSPO were obtained as gift samples from Reddy's Laboratories. All other chemicals used were of analytical grade.

Methods

Pre-formulation studies

It is one of the important prerequisite in the development of any drug delivery system. Pre-formulation studies were performed on the drug, which include melting point determination, partition coefficient, and compatibility studies.

Standard graph of VFH in phosphate buffer pH 6.8

Standard stock solution of venlafaxine (1 mg/ml) was prepared by dissolving 100 mg of VFH in 100 ml of phosphate buffer pH 6.8. Diluting the standard stock solution with phosphate buffer pH 6.8, the solution of 100 μg/ml concentration was prepared. From this solution, dilutions were made with phosphate buffer pH 6.8 to get 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 μg/ml concentrations. The absorbance of these solutions was recorded in accordance with Beers' law at λ_{max} 225 nm against phosphate buffer pH 6.8 as blank using ultraviolet (UV)-visible spectrophotometer (Elico SL 164) and standard graph of venlafaxine was plotted (Fig. 1).

Determination of melting point

Melting point of the drug was determined by taking a small quantity of VFH in a capillary tube (fused at one end). The capillary tube was placed in a melting point apparatus and the temperature at which drug melts was recorded. This was performed thrice and the average value was noted [7].

Partition coefficient determination

The partition coefficient (log P) is a measurement of lipophilicity of molecules, which can be used to predict its capability to cross the biological membrane. The partition coefficient studies were performed using n-octanol as non-aqueous phase and phosphate buffer pH 6.8 as aqueous phase [8]. The two phases were mixed in equal quantities (10 ml each) and kept for saturation with each other in separating funnel. After mixing the system, remain undisturbed for half an hour. About 10 mg of drug added to this solution and was shaken. After shaking, the resulting solution was kept aside for 24 hrs. Then, the two phases were separated and the aqueous phase was filtered, suitably diluted and the amount of VFH in the aqueous phase was determined by measuring absorbance at 225 nm using UV-Visible spectrophotometer (Elico SL 164).

Drug-excipient compatibility study

In the process of patch formation, drug, and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers.

Fourier transform infrared (FTIR) spectra of pure VFH, HPMC E50cps, Eudragit RSPO, PVP K-90, citric acid, and a mixture of drug and polymers were carried out by FTIR spectrophotometer. The IR spectrum of the drug was compared with that of the physical mixture to check for any possible drug-excipient interaction [9].

In vitro permeation of pure drug solution

The *in vitro* drug permeation studies were carried out by using a modified Franz diffusion cell (50 ml) across a dialysis membrane 50 KD (Hi Media) with a cross-sectional area of 3.8 cm^2 [10]. The receptor compartment was filled with phosphate buffer pH 6.8 and donor compartment contained 1 mg/ml concentration of drug in phosphate buffer pH 6.8 [11]. The whole assembly was kept on a magnetic stirrer, and solution in the receiver compartment was constantly and continuously stirred throughout the experiment using magnetic beads. The temperature of the system was maintained at 32.0±0.5°C. At suitable time intervals, aliquots (2 ml) were collected and the diffusion medium of the same volume (2 ml) was then replaced into the receptor compartment. Suitably, diluting the aliquot with phosphate buffer pH 6.8, the absorbance of samples was measured at 225 nm using a double beam UV-visible spectrophotometer (Elico SL 164). The amount of drug permeated per square centimeter at each time interval was calculated from the absorbance of aliquots and plotted against time.

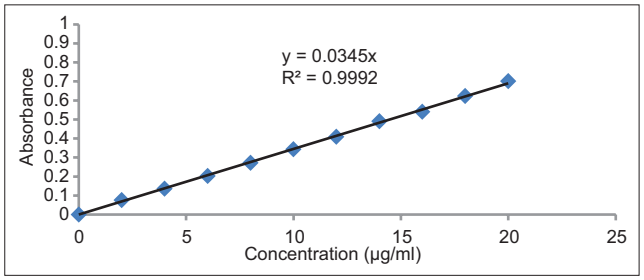

Fig. 1: Standard graph of venlafaxine hydrochloride in phosphate buffer pH 6.8

Formulation development

Preliminary screening

Initial trials were done by preparing monolayer and then bilayer transdermal patches with different combination of polymers and by increasing their concentrations. Bilayer patches showed better retarding ability when compared to monolayer patches but with a drawback of the brittleness of secondary layer and separation of two layers during long-term storage. For binding of two layers, a layer of PVP K-90 (100 mg) as a binding layer was incorporated whereas to overcome brittleness, solid plasticizers like vitamin E, citric acid were tried [12].

Preparation of tri-layer VFH transdermal patches

Tri-layered adhesive dispersion type transdermal patches were prepared by solvent evaporation technique with HPMC E50cps as drug reservoir, Eudragit RSPO as a rate-controlling membrane, PVP K-90 as binding layer and citric acid (30%w/w) as plasticizer.

The polymeric solution of HPMC E50cps was prepared in 25 ml of the solvent mixture (chloroform and methanol, 1:1). To this, previously prepared solution of venlafaxine and citric acid in 10 ml of solvent mixture was added and set aside for 2 hrs to remove entrapped air, transferred to a Petri plate of diameter 9 cm and dried at room temperature. The binding layer was prepared by solubilizing PVP K-90 and citric acid in 15 ml of the solvent mixture and was poured over dried primary layer. The rate controlling membrane was prepared by dissolving Eudragit RSPO and citric acid in 15 ml of the solvent mixture and poured over the already dried film. It was then allowed for drying at room temperature. The developed patches were removed carefully, cut to size (each having an area of 3.8 cm^2 and 25 mg of drug), wrapped in aluminum foils and stored in the desiccators till further evaluation [13,14]. The composition of patches was shown in Table 1.

Patches were subjected to physicochemical evaluation such as appearance, thickness, flatness, weight uniformity, drug content, folding endurance, percentage moisture loss, percentage moisture absorption, water vapor transmission rate, *in-vitro* drug release, *in-vitro* permeation, skin irritation, and stability studies.

Evaluation of transdermal patches

Physical appearance

All the prepared patches were visually inspected for color, clarity, flexibility, and smoothness [15].

Folding endurance

The patch was folded in the center between the finger and thumb and then opened. This was called "one folding." The procedure was repeated till a crack appeared or breakage of the patch occurred. The total number of folds till the break denoted the folding endurance value [16].

Thickness

The thickness uniformity of the patch was assessed by measuring thickness at three different points using a digital screw gauge and average thickness was taken as the thickness of patch [17].

Table 1: Formulation design of VFH transdermal patches[a]

Formulation code	Drug reservoir (mg)		Rate controlling membrane
	Drug	HPMC E50cps	Eudragit RSPO (mg)
F1	400	2000	250
F2	400	2000	500
F3	400	2000	750
F4	400	2000	1000

VFH: Venlafaxine hydrochloride, HPMC: Hydroxypropyl methylcellulose

Weight uniformity

For each formulation, three randomly selected patches were weighed individually on a digital balance [18] and the average weight was calculated.

Flatness

From each transdermal patch, longitudinal strips were cut, one from the center and two from the either side and length was measured. This measurement was taken for 3 days and the constriction of the strips was considered. The variations in the length due to non-uniformity in flatness were measured by determining percent constriction, considering 0% constriction is equivalent to 100% flatness [19,20].

$$\%\text{Constriction} = \frac{L1 - L2}{L1} \times 100 \quad (1)$$

Where, L1=Initial length of each strip and L2=Final length of each strip.

Drug content

Drug content estimation was carried out in triplicate on each formulation. Each patch from different formulations was taken, cut into small pieces and was added to a beaker containing 100 ml of phosphate buffer pH 6.8. It was then stirred on a magnetic stirrer and filtered. From the filtrate, 1 ml was withdrawn and diluted to 10 ml with phosphate buffer pH 6.8 and the absorbance was measured at λ_{max} 225 nm using UV-visible spectrophotometer (Elico SL 164) against phosphate buffer pH 6.8 as blank and the concentration was calculated. By correcting the dilution factor, the drug content was determined [21].

Moisture content

The patches were weighed individually and kept in a desiccators containing calcium chloride at room temperature for 24 hrs. The final weight was noted when there was no further change in the weight of patch [22]. The percentage of moisture content was calculated by using the following formula:

$$\text{Percentage moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100 \quad (2)$$

Moisture absorption

The patches were weighed accurately and placed in the desiccators containing a saturated solution of potassium chloride to maintain 80-90% RH. After 3 days, the patches were taken out and weighed again. The study was performed at room temperature [23]. The percentage moisture absorption was calculated using the formula:

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100 \quad (3)$$

Water vapor transmission rate studies (WVTR)

For this study, vials of equal diameter were used as transmission cells. These vials were washed thoroughly and dried in an oven. About 1 g of fused calcium chloride was taken in the vials and the polymeric patches were fixed over the brim with the help of an adhesive tape. Then the vials were weighed accurately and kept in the closed desiccators containing saturated solution of potassium chloride to maintain 80-90% RH [24,25]. The vials were taken out and weighed at 24 hrs time intervals to note down the weight gain until they show a constant weight (7 days). The rate of water vapor transmitted was found using following formula:

$$\text{WVTR} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Exposed time} \times \text{Surface area}} \quad (4)$$

In-vitro drug release study

The drug release from the prepared transdermal patches was studied using USP type II dissolution test apparatus (Electro lab TDT-06L). Patches were designed to release the drug from one side only. The assembly for release studies was prepared by sandwiching the patch between dialysis membranes 50 KD (Hi Media). A piece of glass slide was placed as support to prevent the assembly from floating. The dialysis tubing with patch inside was secured from both ends using dialysis closure clips. Patch assembly was then placed carefully at the bottom of the vessel and centered using a glass rod and vessel was closed with a lid. The dissolution medium was 500 ml of phosphate buffer pH 6.8 at 32±0.5°C (the skin surface temperature) and paddle speed was set at 25 rpm. Samples of 5 ml were collected at predetermined time intervals for 24 hrs and were replenished with 5 ml of fresh medium. The withdrawn samples were analyzed spectrophotometrically (Elico SL 164) at 225 nm. The content of venlafaxine was calculated from the standard curve. The cumulative drug release were calculated and plotted against time for different formulations [26,27]. The experiment was performed in triplicate and the mean±standard deviation value was calculated.

Kinetics of in-vitro drug release

In order to understand the drug release kinetics of optimized patch, the % cumulative drug release data of the *in-vitro* dissolution study were analyzed with various kinetic models such as zero order, first order, Higuchi, Peppas and Hixson-Crowell model [28,29]. By comparing the correlation co-efficient values obtained, the best-fit model was selected.

***In-vitro* permeation study**

In-vitro permeation studies were performed on optimized formulation by using a modified Franz diffusion cell (50 ml) across a dialysis membrane 50 KD using phosphate buffer pH 6.8 as the *in-vitro* study fluid in the receptor compartment. The transdermal patch was placed in intimate contact with the dialysis membrane. The temperature of the diffusion cell was maintained at 32±0.5°C. The whole assembly was kept on a magnetic stirrer, and solution in the receiver compartment was constantly and continuously stirred throughout the experiment using magnetic beads. The samples were withdrawn (2 ml each time) at predetermined time intervals for 24 hrs and an equal amount of phosphate buffer pH 6.8 was replaced each time. The samples were analyzed for drug content by using UV-visible spectrophotometer (Elico SL 164) at 225 nm. The amount of drug permeated per square centimeter at each time interval was calculated and plotted against time in hrs [30,31]. The study was performed in triplicate.

Permeation data analysis

Drug flux (J) at steady state was calculated from the slope of the plot of the cumulative amount of drug permeated (μg/cm^2) at steady state against time using linear regression analysis [32].

$$J = \frac{dQ}{dt} \times \frac{1}{A} \quad (5)$$

The steady state permeability coefficient (Kp) of the drug was calculated by using the following equation:

$$Kp = \frac{J}{C} \quad (6)$$

Where, J=Steady state flux
C=Concentration of VH in donor compartment
A=Effective diffusion area
dQ/dt=Steady state slope

Skin irritation study

The patches were tested for their potential to cause skin irritation/sensitization in healthy human volunteers. Placebo patches of area 3.8 cm^2 were applied to the 12 healthy volunteers and observed for any sign of redness, itching, erythema, and edema for a period of 24 hrs [33].

Stability studies

Optimized medicated patches were subjected to short-term stability testing as per ICH guidelines Q1F for zones III and IV. The transdermal patches were stored at accelerated test conditions (40±2°C and 75±5% RH) in stability chamber for 3 months [34]. The patches were analyzed for physical appearance, folding endurance, flatness, % drug content, and *in vitro* drug release study by the procedure stated earlier.

RESULTS AND DISCUSSION

Preformulation studies

The melting point was found to be 217°C. This value is in good agreement with those reported in the literature. The log P of venlafaxine was found to be 2.7 which indicate that the drug has sufficient lipophilicity and meets the requirements of formulating it into a transdermal patch.

Compatibility study

The possible interaction between the drug and the polymers used was studied by FTIR spectroscopy. IR spectra of pure venlafaxine showed characteristic peaks at wave numbers 3347/cm (O-H stretching), 1613/cm (N-H stretching), 3016/cm (aromatic C-H stretching), 2935/cm (alkane C-H stretching). All the combinations containing drug and polymer shows same or slightly shift in peak values when compared with the characteristic peak values of the pure drug. The final formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components (Figs. 2 and 3).

***In-vitro* permeation of pure drug solution**

The *in-vitro* permeation study was performed with Franz diffusion cell. The cumulative amount of VFH permeated in 24 hrs was found to be 643.63±2.26 µg/cm^2 (Fig. 4) and the flux was calculated to be 4.44 µg/cm^2/hr with permeability coefficient of 4.44×10^{-3} cm/hr.

Preparation and evaluation of tri-layered VFH transdermal patches

Initial trials were done by preparing monolayer patches with different combination of polymers and by increasing their concentrations such as HPMC E50cps, Gantrez, hydroxyl propyl cellulose (HPC JF), poly vinyl alcohol, sodium alginate, sodium carboxymethyl cellulose 25cps, and PVP K-30. Drug release from monolayer patches was not adequate. Trials were done by preparing bi-layered patches using Eudragit RL100, Eudragit RLPO, and RSPO as a hydrophobic secondary layer. Among these, only Eudragit RSPO has better-retarding ability but has a drawback of the brittleness of secondary layer and separation of two layers during long-term storage. For binding of two layers, PVP K-90 (100 mg) as a binder was incorporated whereas use of solid plasticizer (Eva and Milan, 2012) [35], citric acid (30%w/w) found to be effective in improving the flexibility of Eudragit RSPO layer. Incorporation of PVP K-90 binding layer further improved the retarding ability. The patches thus prepared showed flexibility with the better retarding release of venlafaxine for 24 hrs at 25 rpm maintained at 32.0±0.5°C.

Physicochemical evaluation

The folding endurance value, thickness, weight, % drug content of all the VFH patches were within the acceptable range. The results of folding endurance indicated that the patches would not break and maintain their integrity with general skin folding when applied. All the patches showed no change in strip length. Thus, percent constriction of all patches was found to be 0% (100% flatness). The WVTR ranged from 5.16×10^{-4} to 6.89×10^{-4} g/cm^2/hr. Maximum WVTR was seen in formulation F1; this was due to the lesser hydrophobic nature of the patch, which allowed more water vapor transmission through this patch compared to the other patches (Table 2).

Moisture absorption and moisture loss studies

The percentage of moisture absorbed ranged from 3.99% to 9.88% whereas moisture loss percentage ranged from 6.10% to 10.71%. It was observed both moisture absorption and moisture loss were decreased as the concentration of hydrophobic polymer increases. Further, it was observed that moisture absorption was less in all the patches than the moisture loss (Fig. 5).

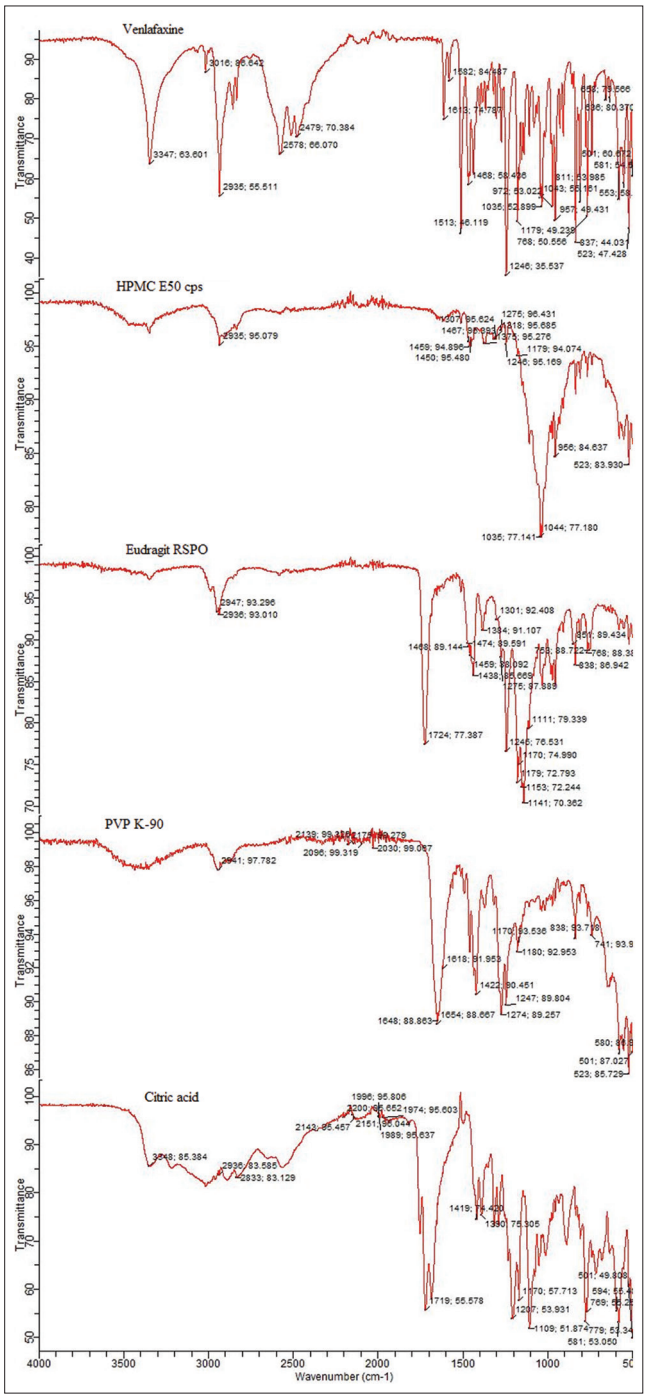

Fig. 2: Fourier transform infrared spectrum of pure drug, hydroxypropyl methylcellulose E50cps, Eudragit RSPO, PVP K-90, and citric acid

***In vitro* drug release studies**

Phosphate buffer pH 6.8 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.999. It was clear from the release profiles of formulations that the drug release was governed by polymer nature and content. The formulations F2 showed the maximum drug release for 24 hrs (96.42%) when compared to other formulations F1, F3, and F4. Hence, F2 formulation was optimized. The release was decreased as the concentration of Eudragit RSPO (hydrophobic polymer) increases (Fig. 6).

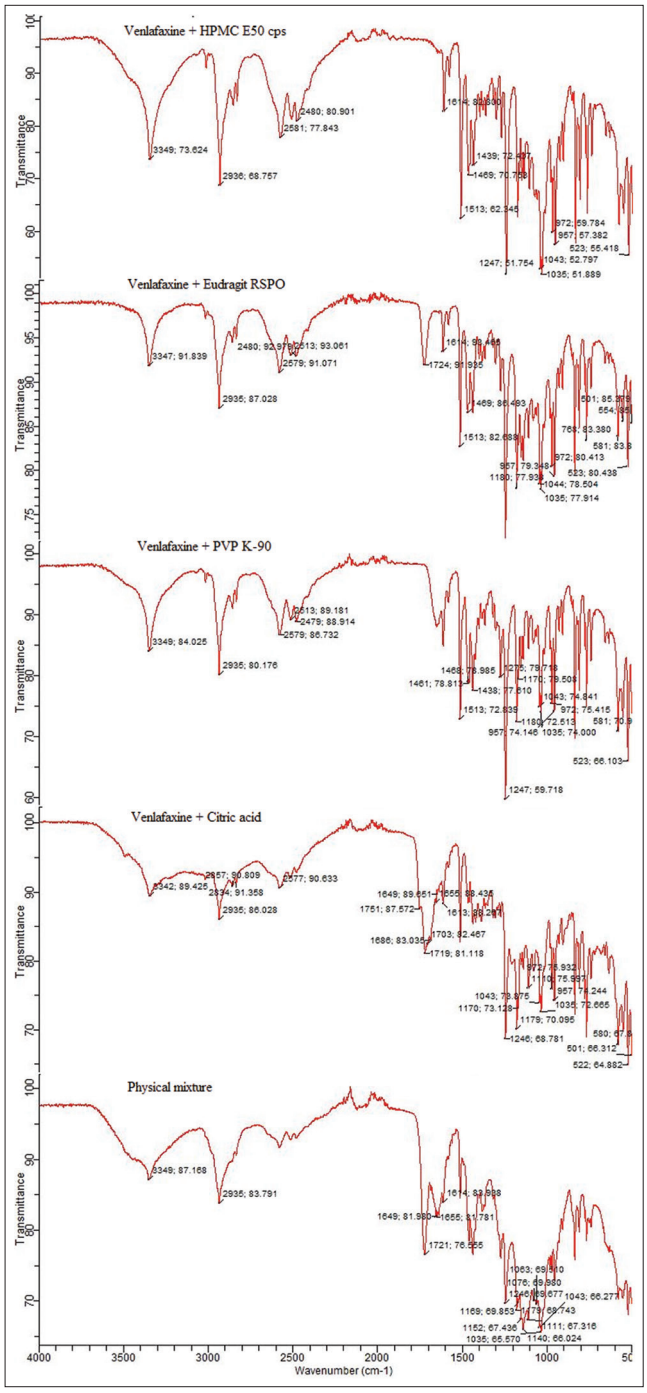

Fig. 3: Fourier transform infrared spectrum of drug + hydroxypropyl methylcellulose (HPMC) E50cps, drug + Eudragit RSPO, drug + PVP K-90, drug + citric acid, and physical mixture (drug + HPMC E50cps + Eudragit RSPO + PVP K-90 + citric acid)

The data obtained from *in vitro* study for optimized formulation F2 were fitted to various kinetic models that are employed to assess the drug release kinetics (34). The results obtained were plotted as drug released versus time. The drug release data showed good fit into Peppas model with R^2 value 0.990 (Table 3). The n-value obtained from Korsmeyer-Peppas model confirmed that the drug release followed Fickian diffusion mechanism.

In vitro permeation study of optimized venlafaxine patch

Based on the release profiles of all formulations, *in vitro* permeation study was carried out on the optimized formulation F2. The results

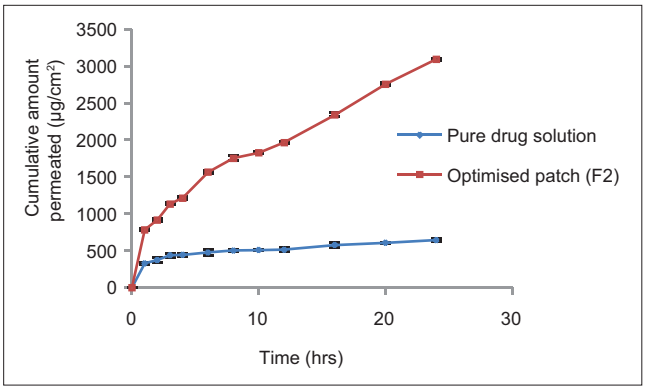

Fig. 4: *In vitro* permeation profile of pure drug solution and optimized venlafaxine hydrochloride patch. Results were expressed in mean±standard deviation (n=3)

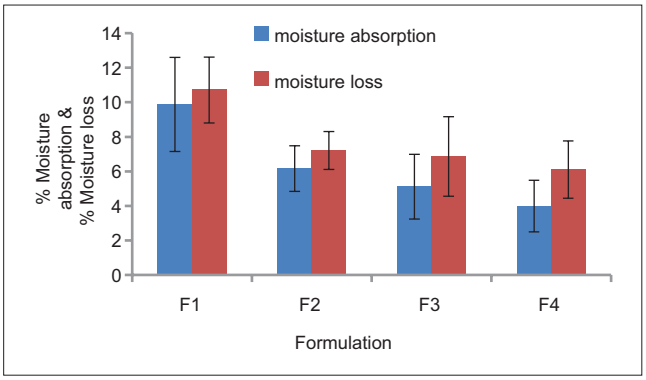

Fig. 5: Moisture absorption and moisture loss studies. Results were expressed in mean±standard deviation (n=3)

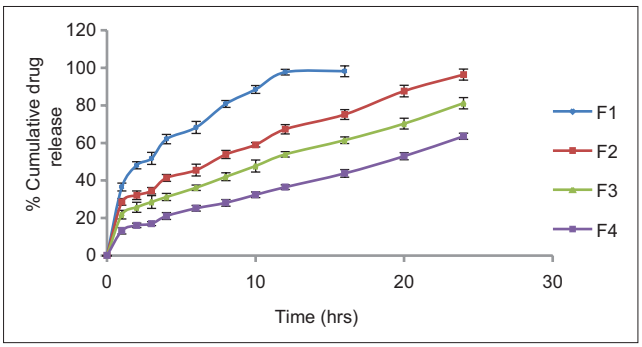

Fig. 6: *In vitro* drug release profile of venlafaxine hydrochloride from transdermal patches, mean±standard deviation (n=3)

indicated that 3094.737±1.38 µg/cm^2/hr drug permeated in 24 hrs from the transdermal patch with a flux of 28.28 µg/cm^2/hr and permeability coefficient of 1.1315×10^{-3} cm/hr (Fig. 4).

Stability studies

Optimized formulations F2 was kept for accelerated stability studies as per ICH guidelines. The results of the stability studies revealed that there was no significant change in flexibility; % drug release and drug content (Table 4). Thus, prepared transdermal patches of VFH possess required stability.

CONCLUSIONS

VFH tri-layered transdermal patches were successfully developed. Based on the results, it was concluded that polymers selected were suitable for designing adhesive type tri-layered transdermal patches of VFH for

Table 2: Physicochemical evaluation of VFH patches

Parameter	Formulation code			
	F1	F2	F3	F4
Weight (mg)	257.06±2.31	268.6±1.32	282.96±4.21	298.7±1.76
Thickness (mm)	0.512±1.13	0.531±0.91	0.556±1.77	0.582±1.42
Folding endurance	286.33±3.12	468.66±2.51	479.33±4.63	538.66±2.76
Flatness (%)	100	100	100	100
Drug content (%)	97.12±1.11	99.54±1.41	98.53±2.12	99.91±1.56
WVTR ($g/cm^2/hr$)	5.16×10^{-4}±0.93	5.32×10^{-4}±1.16	6.10×10^{-4}±1.32	6.89×10^{-4}±2.09

Results were expressed as mean±SD (n=3). SD: Standard deviation, WVTR: Water vapor transmission rate, VFH: Venlafaxine hydrochloride

Table 3: Drug release kinetics of optimized transdermal patch (F2)

Model fitting	r^2
Zero order	0.919
First order	0.913
Higuchi matrix	0.987
Peppas	0.990
Hixson-Crowell	0.965

Table 4: Stability studies of optimized formulation (F2) for 3 months

Time in days	Drug content (%)	Folding endurance	Physical appearance	% Cumulative drug release
0	99.54	468.66	No change in color	96.42
90	97.1	451.12	Slight yellowish color	95.12

controlled drug delivery. Citric acid worked as a suitable plasticizer for VFH tri-layered patches. The release from patches depends mainly on the concentration of hydrophobic polymer (Eudragit RSPO). Thus, the developed tri-layered transdermal patches of VFH could perform better than other dosage forms, leading to improved efficacy and better patient compliance.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Reddy's laboratories, Hyderabad for gift samples of HPMC E50cps, Eudragit RLPO, Eudragit RSPO, and Eudragit RL100 and are also thankful to Hercules Inc, USA for providing gift sample of HPC.

REFERENCES

1. Vyas SP, Khar RK. Controlled Drug Delivery Concepts and Advances. New Delhi: Vallabh Prakashan; 2002.
2. Arti K, Kumar YA, Sunil S, Gautam H, Haribansh NS, Anamika S, *et al*. Theoretical aspects of transdermal drug delivery system. Bull Pharm Res 2013;3(2):78-89.
3. British Pharmacopoeia. Vol. 2. United Kingdom: The Stationery Office; 2008. p. 2242.
4. Available from: http://www.drugbank.ca/drugs/DB00285. [Last accessed on 2013 Feb 13].
5. Madhavi BB, Nath AR, David B, Ramalingam R, Madhu MN, Arjun G, *et al*. Formulation and evaluation of venlafaxine HCL enclosed in alginate microbeads prepared by iontophoretic gellation method. Int J Pharm Res Dev 2009;8:1-11.
6. Sweetman SC. Martindale: The Complete Drug Reference. London: Pharmaceutical Press; 2009.
7. Available from: http://www.chem.ucalgary.ca/courses/351/laboratory/meltingpoint.pdf. [Last accessed on 2013 Mar 21].
8. Gajanan D, Kumar JD, Kumar PV. Formulation and evaluation of transdermal drug delivery system of clopidogrel bisulfate. Asian J Pharm Life Sci 2011;1(3):269-78.
9. Suchika S, Geeta A, Sanju D. Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers. Der Pharm Lettre 2010;2(6):84-98.
10. Naseera K, Sajeeth CI, Santhi K. Formulation, optimization and evaluation of matrix type of transdermal system of simvastatin using permeation enhancers. Int J Curr Pharm Res 2012;4(2):79-87.
11. Kumar MP, Prasad MR, Pramod M, Reddy VP. Effect of permeation enhancer on *ex-vivo* permeation of ondansetron HCL buccal tablets. Int J Pharm Sci Res 2011;2(11):2841-5.
12. Prajapati ST, Patel CG, Patel CN. Formulation and evaluation of transdermal patch of repaglinide. ISRN Pharm 2011;2011:651909.
13. Madishetti SK, Palem CR, Gannu R, Thatipamula RP, Panakanti PK, Yamsani MR. Development of domperidone bilayered matrix type transdermal patches: Physicochemical, *in vitro* and *ex vivo* characterization. Daru 2010;18:221-9.
14. Tanwar YS, Chauhan CS, Sharma A. Development and evaluation of carvedilol transdermal patches. Acta Pharm 2007;57(2):151-9.
15. Shivaraj A, Selvam RP, Mani TT, Sivakumar T. Design and evaluation of transdermal drug delivery of Ketotifen fumarate. Int J Pharm Biomed Res 2010;1(2):42-7.
16. Alka V, Bhupesh V, Sunil P, Kishu T. Formulation and evaluation of transdermal therapeutic system of matrix type clonidine hydrochloride. Der Pharm Lettre 2012;4(4):1137-42.
17. Amish AD, Zankhana PS, Janki J. Formulation and evaluation of transdermal ondansetron hydrochloride matrix patch: *In-vitro* skin permeation and irritation study. Int J Pharm Res Allied Sci 2012;2:26-34.
18. Teja AR, Hemant KS, Swetha S, Prasad MS. Preparation and evaluation of transdermal patches of metformin hydrochloride using natural polymer for sustained release. Int J Pharm Pharm Sci 2012;4(3):297-302.
19. Vidyavati S, Jithan A. Development and evaluation of zero order sustained release matrix type transdermal films of ibuprofen. J Glob Pharma Technol 2010;2(2):51-8.
20. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in vitro* and *in vivo* characteristics. AAPS PharmSciTech 2007;8:2.
21. Dhawal D. Formulation and *In-vitro* evaluation of transdermal patches of methyl salicylate. Int J Pharm Technol 2012;4(2):4208-17.
22. Madhura SD, Sheelpriya RW, Abhay MI. Development and characterization of transdermal patches of ondansetron hydrochloride Int J Pharm Pharm Sci 2012;4(5):293-8.
23. Kumar KJ, Muralidharan S, Dhanaraj SA. Formulation and *in vitro* evaluation of terbinafine HCL transdermal patches. J Pharm Sci Res 2012;4(6):1840-3.
24. Kulkarni VH, Keshavayya J, Shastry CS, Preeti V, Kulkarni. Transdermal delivery of antiasthmatic drug through modified chitosan membrane. Indian J Pharm Sci 2005;67(5):544-7.
25. Muzib YI, Lavanya T. Design and evaluation of stavudine transdermal patches using hydrophilic and hydrophobic polymers. J Pharm Res 2012;5(2):1176-82.
26. Prasad Verma PR, Chandak AR. Development of matrix controlled transdermal delivery systems of pentazocine: *In vitro/in vivo* performance. Acta Pharm 2009;59:171-86.
27. Vishnu YV, Kishan V, Rao YM. Enhanced bioavailability of nimodipine from bioadhesive buccal bilayered patches in human volunteers. Br J Pharm Res 2013;3(4):1015-30.
28. Dash S, Murthy PN, Nath L, Chowdhury P. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm 2010;67:217-23.
29. Yogesh MA, Rupesh VC, Updesh BL, Dinesh MB, Milind JU. Design, formulation and evaluation of transdermal drug delivery system of budesonide. Dig J Nanomater Biostruct 2011;6(2):475-97.

30. Saumya D, Dharmajit P, Prasad SN. Optimization and evaluation of terbutaline sulphate transdermal film. Int J Pharm Technol 2011;3(4):3612-7.
31. Anisree GS, Ramasamy C, John C, Wesley I. Design and evaluation of domperidone transdermal films. J Pharm Res 2012;5(8):3942-4.
32. Mitali G. Formulation and evaluation of transdermal patch of an antihypertensive drug. Pharma Sci Monit 2013;4(1):3664-82.
33. Kunal NP, Hetal KP, Vishnu AP. Formulation and characterization of drug in adhesive transdermal patches of diclofenac acid. Int J Pharm Pharm Sci 2012;4(1):296-9.
34. Amit KV, Om PM, Nimisha Dipti S. Formulation and evaluation of transdermal patch containing turmeric oil. Int J Pharm Pharm Sci 2012;4(5):358-61.
35. Eva Snejdrova and Milan Dittrich .Pharmaceutical Application of plasticized polymers in : Recent Advances in Plasticizers. Edited by Mohammad Luqman. Published by In TECH 2012; 69-90.