Journal of Scientific and Innovative Research 2014; 3 (1): 49-59
Available online at: www.jsirjournal.com

Research Article

ISSN 2320-4818
JSIR 2014; 3(1): 49-59

Received: 30-11-2013
Accepted: 31-01-2014

Prakash Katakam
Faculty of Pharmacy, University of Zawia, Az-Zawiyah, Libya

Maninder B.V. Reddy
Nirmala College of Pharmacy, Mangalagiri, Guntur, India

Nagiat T. Hwisa
Faculty of Pharmacy, University of Zawia, Az-Zawiyah, Libya

Fathi H. Assaleh
Faculty of Pharmacy, University of Zawia, Az-Zawiyah, Libya
.
Baishakhi Dey
School of Medical Science & Technology, IIT Kharaghpur, India

Satyanarayana V. Murthy
University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Guntur, India

Babu R. Chandu
Faculty of Pharmacy, University of Zawia, Az-Zawiyah, Libya

Shanta K. Adiki
Nirmala College of Pharmacy, Mangalagiri, Guntur, India

Correspondence:
Dr. Prakash Katakam
Faculty of Pharmacy, University of Zawia, Az-Zawiyah, Libya
Tel: +218-926855775
E-mail: pkatakam9@gmail.com

Formulation and evaluation of sustained release venlafaxine tablets using hydrophilic-hydrophobic polymer combinations by melt granulation

Prakash Katakam, Maninder B.V. Reddy, Nagiat T. Hwisa, Fathi H. Assaleh, Baishakhi Dey, Satyanarayana V. Murthy, Babu R. Chandu, Shanta K. Adiki*

Abstract

The current research aims to formulate Venlafaxine Sustained Release (VHL-SR) tablets using hydrophilic-hydrophobic polymers combination blends by melt granulation technique which highlights the novelty. The polymers selected for the present study have matrix forming properties. Results of FTIR studies have shown that there were no interactions between the polymers used and the drug VHL. Various formulations of VHL- SR tablets (F1-F16) using different combinations of hydrophilic and hydrophobic polymers viz. Carbopol 71G, HPMC K15M, PEO, sodium CMC, Eudragit RS100 and precirol were formulated. Prior pre-formulation studies carried out on powder blend showed good flow properties.
Routine quality evaluations of the VHL-SR tablets showed the diameter of the tablets of all formulations were found to be 9.0±0.0 mm and thickness ranged between 2.08±0.08 to 2.25±0.14 mm, hardness 4.08±0.20 - 5.50±0.31 kg/cm^2, percentage friability 0.24±0.03 - 0.45±0.01%, weight variation from 0-1.15%, drug content uniformity from 98.17±0.68 to 101.89±0.73%, all within Pharmacoepial limits. Results of *in-vitro* drug release study indicated that the formulation containing Carbopol 71G (50 mg), Xanthan gum (75 mg) and MCC (50 mg) extended the release of the VHL. Formulation F15 was the optimized one which gave satisfactory release (95.2%) for 16 hr and with a similarity factor (f2) 68.46, the release kinetics best explained by the Korsmeyer-peppas and Higuchi diffusion models. The "N" values between 0.5-1.0 in all the formulations exhibiting a non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism. The formulation showed appreciable stability under accelerated conditions after 2 m.

Keywords: Melt granulation technique, Polymers, Pre-formulation, FTIR, Higuchi diffusion models, Non-Fickian.

Introduction

Oral route is the most commonly adapted and convenient route for drug delivery because of flexibility in the formulation, patient compliance and physician's convenience for dose adjustment. Most of the conventional dosage formulations are immediate-release systems where there is no stringent control over drug release and often results in multiple dosing, leads to fluctuations in plasma drug concentration.[1-6] Moreover to achieve effective concentration at the targeted site of action, intermittent drug intake becomes necessary and often sub or supra therapeutic drug concentrations results in unpredicted side effects. To overcome all these, Sustained Release Dosage Formulations (SRDF) are gaining popularity where the initial release of drug is

sufficient to provide a therapeutic dose soon after administration and then sustained release is obtained over an extended period. It has advantages of reduced incidences of drug-plasma level fluctuations; reduction in dosing frequency enhanced patient, reduction in adverse side effects. Again SRDF is very suitable to target chronic diseases and attainment of effective control over absorption, distribution, metabolism and elimination (ADME) profile of the drug. One of the common ways of controlling drug release pattern is incorporating the drug into the hydrophilic or lipophilic polymer matrix.[4, 6-10]

Venlafaxine hydrochloride (VHL), chemically 1-[2-(Dimethylamino) -l- (p-methoxyphenyl) ethyl] cyclohexano hydrochloride is a oral antidepressant drug, used for the treatment of Major Depressive Disorder (MDD) and Social Anxiety Disorder (SAD) also known as Social Phobia. VHL is referred to as a serotonin-nor-epinephrine-dopamine reuptake inhibitor. It works by blocking the transporter "reuptake" proteins for key neurotransmitter, Serotonin-15-hydroxy tryptamine and nor-epinephrine, thus leaving more active neurotransmitter in the synapse.[11-14] After oral administration, VHL is readily absorbed from gastrointestinal tract, undergoes extensive first pass metabolism in the liver to the active metabolite O-des-methylvenlafaxine. Peak plasma concentration of VHL and O-desmethylvenlafaxine are about 2 and 4 hr respectively with low degree of plasma protein binding. The mean elimination half life of venlafaxine is 5 hr. The usual dose is 75 mg daily with maximum of 375 mg. [8, 9, 15-17]

The current research aims to formulate VHL containing sustained release (SR) tablets using hydrophilic-hydrophobic polymers by melt granulation technique using different combinations of hydrophilic and hydrophobic polymers viz. Carbopol 71G, HPMC K15M, PEO, sodium CMC, Eudragit RS100 and Precirol which have not been tried earlier with prior pre-formulation studies, prescribed quality control evaluations for tablets and in vitro drug (VHL) release kinetic studies.

Materials and Methods

Reagents

All chemicals used were of analytical grade purchased from Merck, Mumbai. Excipients and polymers (Carbopol-71GNF, Precirol, Xanthum Gum, HPMC K15M, Lactose, Magnesium Stearate, Potassium Dihydrogen Phosphate, Polyethylene oxide, Eudrajit 100, Micro crystalline cellulose, Sodium Hydroxide, Aerosil) of pharmaceutical grade were procured from Pharma Train Pvt. Ltd.

Instruments

Electronic balance (Shimadzu BL-220H, Japan); Bulk density apparatus (Indolab VTAP/MATIC-II, India); Standard sieve 30# (Jayant scientific, India); Hot air oven(Chemi Equipments, India); Tablet compression machine (Cadmach, Ahmadabad, India); Friability apparatus (Veego scientific VFT-DV, India); Hardness tester (Monsanto, India); Vernier caliper (Indolab, MITUTOYO, Japan); USP Type I tablet dissolution apparatus (LABINDIA DS 8000); UV spectrophotometer (Thermo Scientific Aquamate plus); Infrared spectroscopy (Thermo Nicolet Nexus 870)

Pre-formulation studies

Identification of the drug (VHL) by organoleptic evaluation, melting point determination, solubility profile were carried out as per literature methods and Indian Pharmacopoeia, 2007.[4, 15-17] The standard calibration curve of VHL for UV spectrophotometric study was carried out in Phosphate buffer media (pH 6.8) at 225 nm as per standard methodology.[18] The percentage purity of VHL was calculated from calibration curve.[4, 12, 13]

Drug-polymers compatibility study by FTIR

An IR spectrum of pure drug (VHL) and properly blended mixtures of VHL with the polymers used were recorded in FTIR spectrophotometer in the scanning range of 500 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. The basic purpose was to observe any changes in the spectrum pattern of the drug due to polymers and thus identify the chances of any chemical interactions.[2, 4]

Evaluations of micromeritic properties of powder blend

The powder blends were evaluated for flow properties by measuring Angle of Repose (fixed funnel method); Bulk Density (BD) and Tapped Bulk Density (TBD) by Cylinder method; Carr's Compressibility Index using the equation: Carr's Compressibility Index (%) = [(TBD-BD)/ TBD] x100; and Hausner's ratio was determined by the equation: Hausner's Ratio = TBD/ LBD. Hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.[1-6, 8-12]

Preparation of sustained release tablets

The sustained release tablets (with binders other than precirol) were prepared by direct compression method using (8mm diameter, round flat faced punches) single punch tablet compression machine. Each tablet contained 75 mg of VHL.

Melt granulation

The binder Precirol was taken in a china dish and heated to 70°C. When the binder started to melt VHL was added and was thoroughly kneaded. The mixture was allowed to cool and solidify. Then the mixture was passed through 30# mesh along with aerosil. Next all other excipients were added to this mixture and the tablets were punched using single punch machine.

Evaluations of tablets

The prepared VHL-SR tablets were evaluated for hardness using Monsanto hardness tester; friability was determined using Roche Friabilator; the thickness and diameter of the tablets were determined using Vernier calipers; weight variation test was carried out as per official methods with the specification limit that not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage.[2-4, 8-12]

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured in UV-vis spectrophotometer at 225 nm. [2-4, 18]

In-vitro drug release study

In-vitro release rate of VHL from the sustained release tablets was carried out using USP Type I rotating paddle apparatus. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). Experimentation was performed at 37ºC ± 0.5ºC with a rotation speed of 50 rpm. 5 mL of samples were withdrawn at one hour intervals and analyzed for VHL content in spectrophotometer at 225 nm. The amount withdrawn was replaced with the same volume of the dissolution media. Experimentation was carried out up to 24 hr. [19-28]

In order to understand the kinetics and mechanism of release of VHL from the SR tablets, the results of the in vitro drug release study were fitted with various kinetic equations like zero order (cumulative percent drug release vs. time); first order (log cumulative percent drug retained vs. time); Higuchi (cumulative percent released vs. √time); Peppas (log of cumulative percent drug release vs. log time). The kinetic model that best fits the dissolution data were evaluated by comparing the regression coefficient values (r) obtained in various models. The N values (release exponent) in Peppas model were used to characterize different release mechanisms, where values of n=0.5 for Fickian diffusion and values between 0.5-1.0 for non-Fickian diffusion and n=1 for zero order.[20-22]

Comparison of dissolution data

The dissolution profiles were further analyzed by difference factor (f1) and similarity factor (f2). Difference factor (f1) is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves.[29, 30] The following equations were used to calculate f1 and f2 values:

$$f1=\{[\Sigma t=1n\ |Rt-Tt|]/[\ \Sigma t=1\ nRt]\}\times 100$$

$$f2=50\ X\ \log\{[1+(1/n)\ \Sigma t=1n(Rt-Tt)2]-0.5\times 100\}$$

where 'n' is the number of points, Rt is the dissolution value of the reference product at time t and Tt is the dissolution value for the test product at time t. For dissolution curves to be considered similar, f1 should be close to zero and f2 should be close to 100. Generally f1 value ranges up to 15 (0–15) and f2 values greater than 50 (50–100) which ensures equivalence between two curves.

In this research VHL-SR that was formulated by us was used as the standard substance and marketed product VENIZ-XR was taken as a reference product. It was manufactured in the form of capsule with coated pellets inside it. It is taken as once daily dose.

HPLC analysis of the VHL-SR tablets

HPLC analysis of the formulated VHL-SR tablets was carried out using C_{18} column (4.6 x 150mm, 3.5 µm ID)

with a flow rate of 0.6 ml per min, 20 µl of injection volume, run time of 8 mins and the UV detector wavelength set at 225 nm.[31]

The mobile phase was prepared by mixing of the 350 mL of phosphate buffer, pH 6.8 with 650 mL of HPLC grade acetonitrile, degassed in ultrasonic water bath for 5 min, filtered through 0.45 µ filter under vacuum filtration. The mobile phase was used as the diluent. VHL working standard and sample solutions were prepared as per reported methodologies.[31] A 20 µL of the standard, sample solutions were injected into the chromatographic system and the area for the VHL peak was measured and the % assay was calculated. Tailing factor for the peak due to VHL Standard solution should not be more than 2.0 Theoretical plates for the VHL peak in Standard solution should not be less than 2000. The percentage of drug content was calculated using the following formula:

$$\text{Assay } \% = \frac{\text{AT}}{\text{AS}} \times \frac{\text{WS}}{\text{DS}} \times \frac{\text{DT}}{\text{WT}} \times \frac{\text{P}}{100} \times \frac{\text{Avg. Wt}}{\text{Label Claim}} \times 100$$

Where, AT = Peak Area of VHL obtained with test preparation, AS = Peak Area of VHL obtained with standard preparation, WS = Weight of working standard taken in mg, WT = Weight of sample taken in mg, DS = Dilution of Standard solution, DT = Dilution of sample solution, P = Percentage purity of working standard.

Stability studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principle of accelerated stability studies was adopted. From the prepared tablets formulation F15 showed appropriate in-vitro drug release and high similarity factor. Hence formulation F15 was selected for the stability study. Stability studies were carried out at 40ºC, 75% Relative Humidity (RH) on the optimized formulation F15 for 2 m. The sustained release tablets were stored at 40ºC, 75% RH in closed high density polyethylene bottles for 1.5 m. The samples were withdrawn after periods of 1 m, and 2 m. The samples were analyzed for its hardness, drug content and in vitro drug release.[8-13]

Results and Discussion

From the point of Organoleptic evaluation, VHL is a white powdery substance, odorless and tasteless. Melting point of VHL was found to be 216.8ºC which complies with the USP specification limits where the melting point range for VHL is between 215-217ºC. VHL was found to be highly soluble in water and methanol. λmax of VHL in phosphate buffer (pH 6.8) was found at 225 nm. VHL showed linearity in the concentration range of 2-10 µg/ml.

The compatibility study between drug (VHL) and excipients or polymers were carried out by Fourier Transforms Infra-Red (FTIR) study. From the Figure 1, it was observed that, peaks due to the major functional group in the spectras of VHL with all the polymers remain unchanged as compared with spectra of VHL alone. So from the above IR interpretations it can be inferred that there was no interaction between VHL and polymers used in the formulations.

The compositions of Venlafaxine Sustained Release Tablets (VHL-SR tablets) are presented in Table 1. Basing on the preformulation studies, details of the micromeritic properties of the powder blend are provided in Table 2. From the results of BD, TBD, Hausner's ratio, Carr's Compressibility Index and Angle of repose it can be inferred that the powder blend exhibited good flow properties. The VHL-SR tablets formulated (F1-F16) didn't show any visual defects like capping, chipping and lamination after punching. The results of physico-chemical evaluations of the VHL-SR tablets (Table 3) showed that tablets indicated good mechanical strength, the percentage friability of all the formulations were found to be less than 1%, percentage deviation from average tablet weight for all the formulations ranged from 0 to 1.15% which are within the Indian Pharmacoepial specified limits. Uniform percentage of VHL content among different batches of tablets was as per limits given in Indian Pharmacopoeia.

In-vitro drug release studies revealed that the release of drug from different formulations varies with the characteristics and composition of matrix forming polymers. The in-vitro cumulative drug release profile of formulations F1, F2, F3, F4 at 12 hr showed 92.96, 93.26, 91.38 and 94.41% drug release respectively and that of the formulations F5, F6, F7 and F8 at 12 hr showed 91.38, 92.88, 92.59 and 96.01% drug release respectively. *In-vitro* cumulative drug release profile of formulations F9-F16 at 12 hr was 86.86, 94.48, 74.06, 70.41, 78.33, 78.33, 75.59 and 82.29% respectively. The release rate of VHL

decreased with decreasing concentration of Carbopol 71G. Carbopol 71G being more hydrophilic than HPMC, swells rapidly; thus decrease of Carbopol 71G content delays the drug release. Drug release rate was increased with increasing amount of hydrophilic polymers. On the other hand both the Carbopol and Xanthan gum decreases the release rate of the drug when their concentration increases. In F14 the release rate is higher than F15. The release rate of F15 decreased as the amount of Xanthan gum is increased. In F15 and F16 the concentration of both the Carbopol and Xanthan gum were same, here the effect of lactose is pronounced, being more hydrophilic the drug release rate gets increased (Figure 2-3).

Further to characterize the release mechanism of VHL from SR tablets, the dissolution data were fitted to different models like zero order, first order, Korsmeyer-peppas and Higuchi diffusion models. The kinetics of VHL release was best explained by the Korsmeyer-peppas and Higuchi diffusion models. The values of "N" (diffusion exponent) were estimated by linear regression of log cumulative % drug release Vs log time (t) of different formulations. The "N" values lies between 0.5-1.0 in all the formulations exhibiting a non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanism. The optimized formulation F15 showed the sustained drug release according to the Higuchi diffusion model (Table 4).

Similarity factor was found by using marketed product VENIZ-XR as a reference product and all other formulations (F1-F16) as test products. The similarity factor for formulation F15 was highest (68.46), and so it was found to be the best optimized formulation (Table 4).

After HPLC analysis, system suitability results showed that tailing factor and theoretical plates obtained from the sample injection were 1.5 and 2674.1 respectively and that obtained after standard injection were 1.4 and 2568.4 respectively. Assay results of VHL tablets showed the content of VHF to be 101.6%.

The results of stability studies of the optimized formulation (F15) after a period of two m are presented in Table 5.

Table 1: Composition of Venlafaxine Sustained Release Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F 9	F10	F11	F12	F13	F14	F15	F16
Venlafaxine	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
HPMC K15M	50	50	-	-	75	75	-	75	75	-	-	-	-	-	-	-
PEO	50	-	-	-	50	-	-	50	-	-	50	50	50	-	-	-
Na CMC	-	50	-	-	-	50	-	-	50	-	-	-	-	-	-	-
Precirol	-	-	75	75	-	-	150	-	-	150	-	-	-	-	-	-
Carbopol 71G	-	-	-	-	-	-	-	-	-	-	-	-	-	50	50	50
Eudragit RS100	-	-	-	-	-	-	-	-	-	-	50	75	75	-	-	-
Xanthum gum	-	-	-	-	-	-	-	-	-	-	-	-	-	50	75	75
MCC	50	50	50	25	50	50	25	-	50	-	50	50	-	50	50	-
Lactose	-	-	-	25	-	-	25	50	-	25	-	-	50	-	-	50
Aerosil	1	1	5	5	2.5	2.5	5	2.5	2.5	5	1	1	1	1	1	1
Mg Sterate	1	1	1	1	1.5	1.5	1	1.5	1.5	1	1	1	1	1	1	1
Total Wt.	227	227	206	206	254	254	281	254	254	256	227	252	252	227	252	252

Table 2: Micromeritic Properties of Powder Blend

Formulation Code	Loose Bulk Density (gm/ml)*	Tapped Bulk Density (gm/ml)*	Hausner's ratio *	Carr's index (%)*	Angle of repose (θ°)*
F1	0.680±0.001	0.788±0.001	1.157±0.001	13.63±0.004	22.33±0.635
F2	0.713±0.006	0.832±0.007	1.166±0.001	14.28±0.007	22.29±1.028
F3	0.680±0.009	0.749±0.009	1.100±0.002	9.09±0.007	24.15±0.350
F4	0.696±0.001	0.809±0.001	1.162±0.001	13.95±0.004	23.48±0.330
F5	0.665±0.008	0.768±0.001	1.153±0.003	13.33±0.002	25.26±0.426
F6	0.730±0.001	0.855±0.006	1.171±0.001	14.62±0.002	22.78±0.203
F7	0.680±0.009	0.768±0.001	1.128±0.001	11.36±0.006	25.18±0.375
F8	0.713±0.001	0.809±0.001	1.135±0.002	11.90±0.008	22.56±1.401
F9	0.713±0.001	0.831±0.002	1.166±0.001	14.29±0.003	24.30±0.462
F10	0.701±0.004	0.805±0.004	1.148±0.002	12.91±0.003	21.38±0.106
F11	0.665±0.003	0.773±0.002	1.162±0.004	13.97±0.008	23.27±0.076
F12	0.687±0.007	0.793±0.006	1.154±0.003	13.36±0.001	22.43±0.759
F13	0.720±0.003	0.853±0.009	1.184±0.001	15.59±0.007	24.65±0.385
F14	0.706±0.009	0.826±0.003	1.169±0.002	14.52±0.005	23.864±0.924
F15	0.689±0.002	0.754±0.005	1.094±0.005	8.62±0.009	22.58±1.084
F16	0.665±0.004	0.734±0.006	1.133±0.003	9.40±0.009	23.48±0.926

*Determination done in triplicate and values expressed in Mean± SE

Table 3: Physico-chemical evaluations of VHL-SR tablets

Code	Dimension		Hardness (kg/cm^2)**	Friability (%)*	Weight variation (%)***	Drug content (%w/w)*
	Diameter (mm)**	Thickness (mm)**				
F1	7.64±0.005	4.50±0.005	4.16±0.25	0.24±0.03	226.66±0.57	101.89±0.73
F2	7.64±0.005	4.6±0	4.33±0.25	0.34±0.07	226.16±0.28	98.67±0.26
F3	7.57±0	4.46±0.005	5.25±0.27	0.40±0.08	206.5±0.86	100.58±0.36
F4	7.57±0	4.46±0.01	4.08±0.20	0.37±0.07	205.6±0.57	98.70±0.55
F5	7.92±0.017	4.64±0.01	5.25±0.27	0.45±0.01	253.96±0.35	98.53±0.41
F6	7.93±0	4.64±0.01	4.33±0.25	0.34±0.04	255.1±1.01	99.53±0.56
F7	7.97±0.011	4.72±0.005	4.41±0.20	0.41±0.03	281.26±0.3	98.20±0.44
F8	7.92±0.005	4.64±0.005	5.16±0.25	0.32±0.10	254.06±0.11	98.96±0.49
F9	7.92±0	4.66±0.011	5.50±0.31	0.33±0.05	253.6±0.52	99.83±0.12
F10	7.93±0	4.68±0	5.16±0.25	0.28±0.07	255.6±0.55	98.22±0.28
F11	7.60±0.011	4.53±0.005	4.33±0.25	0.42±0.03	227±0	98.47±0.21
F12	7.88±0.01	4.62±0.011	5.25±0.27	0.28±0.01	251.63±0.32	99.21±0.76
F13	7.90±0.011	4.61±0.005	4.23±0.40	0.39±0.07	251.73±0.46	98.78±0.29

F14	7.61±0.017	4.55±0	5.25±0.27	0.27±0.01	226.33±1.15	99.29±0.81
F15	7.9±0	4.57±0	4.33±0.25	0.45±0.05	251.93±0.20	99.11±0.19
F16	7.89±0.005	4.56±0.005	5.41±0.20	0.28±0.07	251.93±0.60	98.17±0.68

*All the values are expressed as mean± SE, n=3. **All the values are expressed as mean± SE, n=6. *** All the values are expressed as mean± SE, n=10.

Table 4: Kinetics of drug release from VHF-SR tablets

Code	Zero order		First order		Higuchi		Korsemeyer-Peppas		f2 values
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (mg $h^{-1/2}$)	R^2	N	
F1	0.8823	4.8547	0.8925	0.2450	0.9927	25.599	0.9959	0.4336	48.97
F2	0.8550	5.0344	0.9311	0.2687	0.9753	23.674	0.9698	0.4847	46.87
F3	0.7043	3.6819	0.9369	0.2321	0.9080	21.58	0.9501	0.2956	34.7
F4	0.7457	4.8242	0.9039	0.2745	0.9303	23.30	0.9528	0.3193	36.47
F5	0.8929	5.0994	0.8587	0.2540	0.9917	24.947	0.9903	0.5017	53.67
F6	0.9046	5.9112	0.9439	0.2800	0.9833	26.783	0.9708	0.5542	53.06
F7	0.8653	5.2733	0.8788	0.3238	0.9840	24.339	0.9855	0.3741	46.97
F8	0.8780	5.7258	0.9401	0.2984	0.9882	26.238	0.9869	0.4903	47.38
F9	0.8717	4.6744	0.8997	0.2795	0.9860	23.097	0.9888	0.3956	53.91
F10	0.8268	5.0556	0.9571	0.3021	0.9662	23.709	0.9773	0.324	42.38
F11	0.9423	4.3944	0.8602	0.2273	0.9830	22.09	0.9704	0.4377	65.99
F12	0.9519	4.5178	0.8359	0.2167	0.9599	22.10	0.9307	0.4512	56.54
F13	0.9404	4.7120	0.8237	0.2358	0.9800	22.297	0.9367	0.4059	66.13
F14	0.9042	4.1788	0.8585	0.3224	0.9860	21.46	0.9739	0.3862	65.86
F15	0.9202	4.6266	0.8187	0.2125	0.9710	21.984	0.951	0.4141	68.46
F16	0.8933	4.5309	0.8606	0.2314	0.9789	22.146	0.9675	0.3819	63.11

K0 = zero order rate constant, K1 = first order rate constant, R2 = correlation coefficient, KH= Higuchi constant, N = Koresmeyer Peppas constant, f2 = similarity factor

Table 5: Stability studies of sustained release tablets

Characteristics	**Initial**	**1 m**	**2 m**
Hardness (kg/cm^2)	4.33±0.07	4.31±0.04	4.36±0.04
Drug content (%mg/tablet)	99.38±0.12	98.87±0.37	98.81±0.12
In-vitro drug release at 10 hour (%w/w)	94.83±1.38	95.54±01.53	95.53±1.90

All data is expressed as mean ±SD, m = month(s)

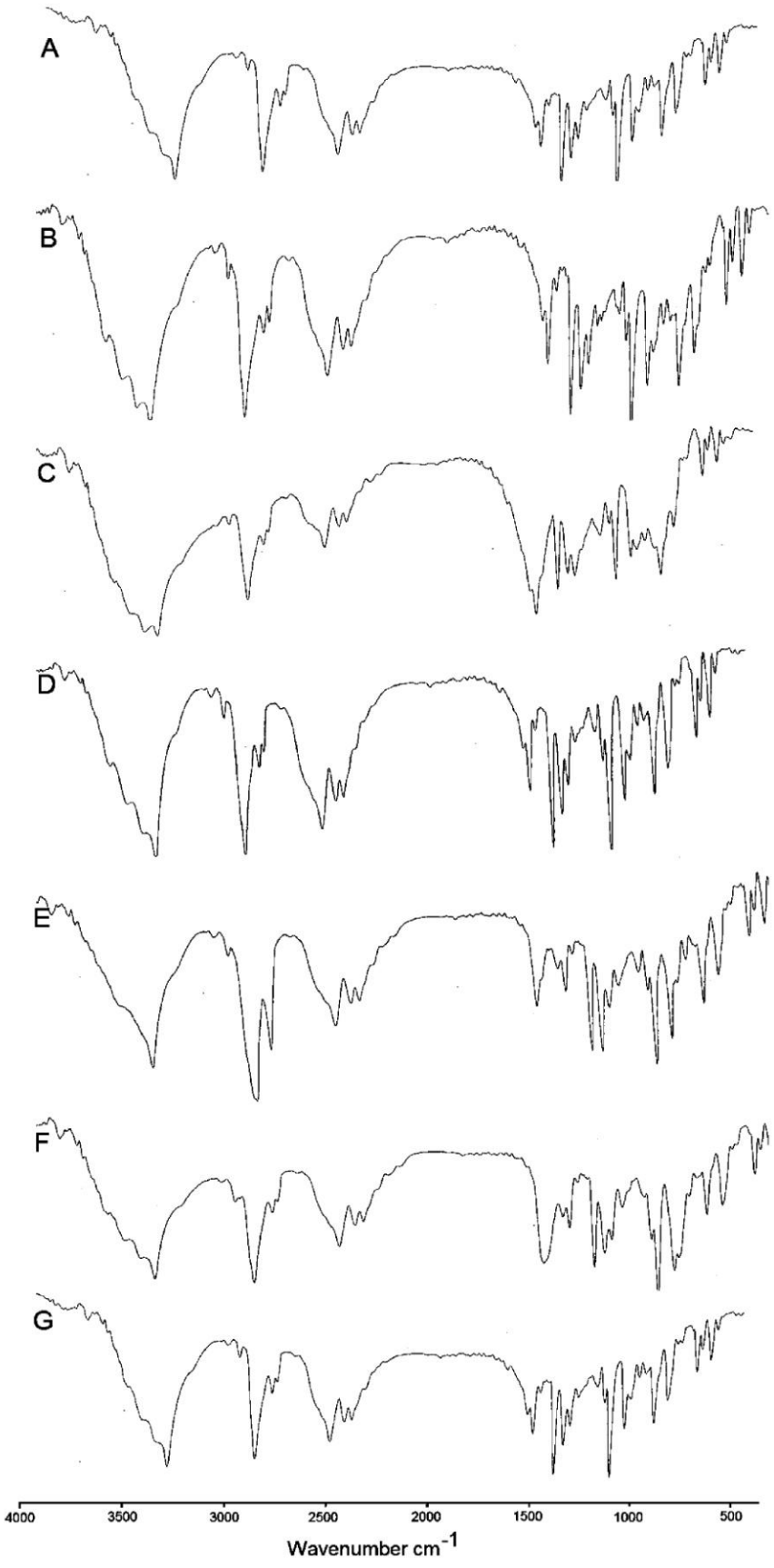

Figure 1: FT-IR spectra of (A) venlafaxine, (B) venlafaxine+ sodium CMC, (C) venlafaxine + PEO, (D) venlafaxine +Precirol, (E) venlafaxine + eudrajit RS100, (F) venlafaxine + carbopol71G and (G) venlafaxine + xanthan gum

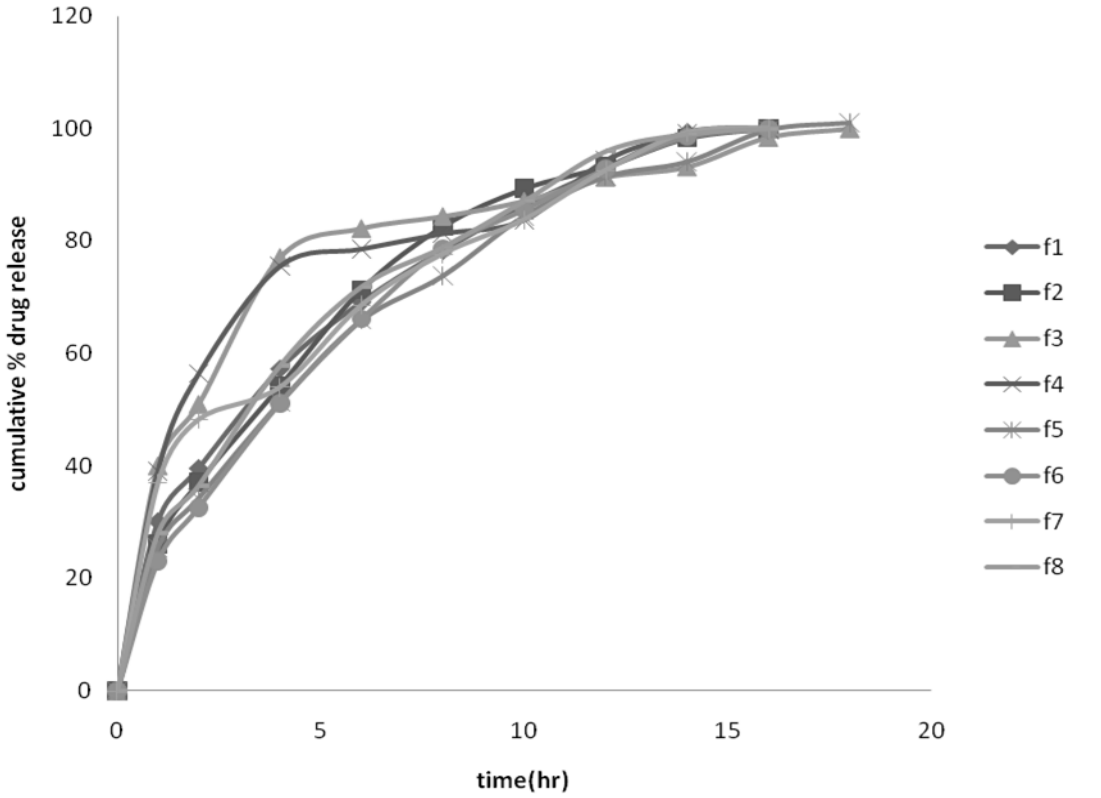

Figure 2: Comparative drug release profiles of formulations F1-F8

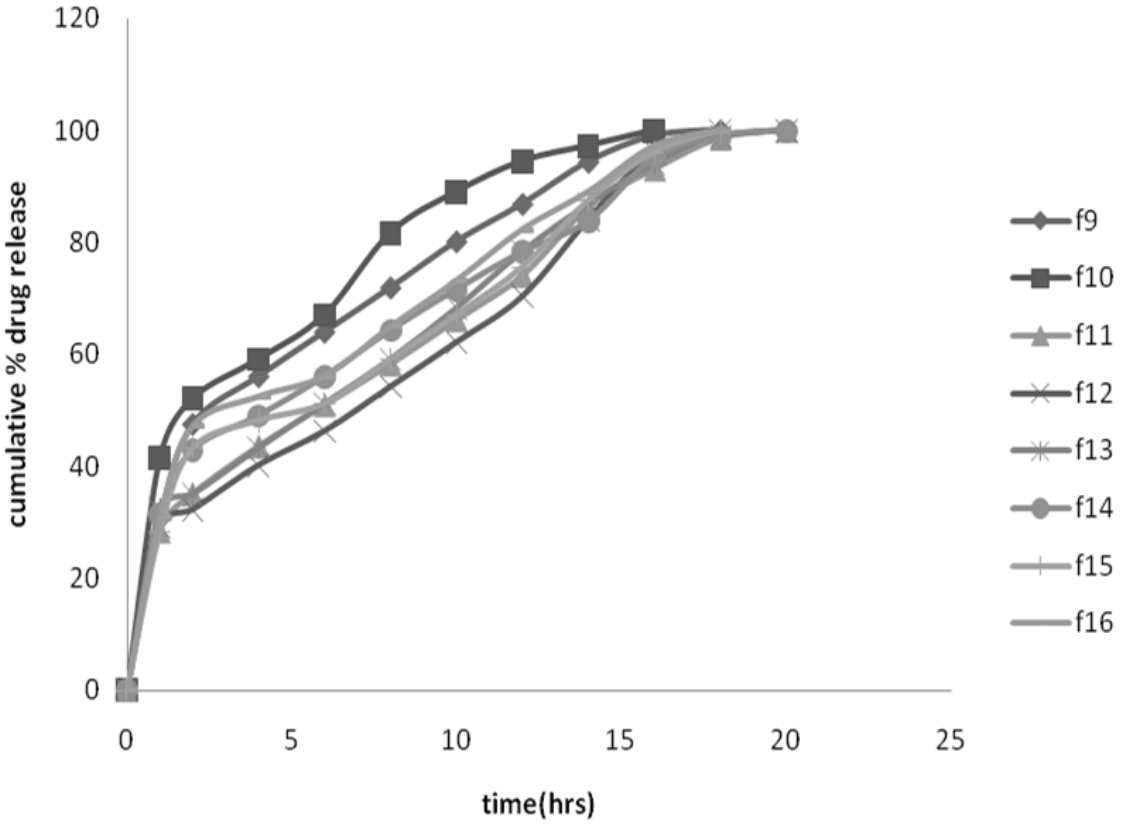

Figure 3: Comparative drug release profiles of formulations F9-F16

Conclusion

VHL is structurally and pharmacologically related to the atypical opioid analgesic tramadol, and also to opioid tapentadol, but not to any of the conventional antidepressant drugs, including tricyclic antidepressants, SSRIs, MAOIs, etc. VHL is having a short half life (5 hr) which makes it a good candidate for the sustained drug delivery system. The polymers selected for the present study have matrix forming properties. Results of FTIR studies have shown that there were no interactions between the polymers used and the drug VHL. Various formulations of VHL SR tablets using different combinations of hydrophilic and hydrophobic polymers viz. Carbopol 71G, HPMC K15M, PEO, sodium CMC, Eudragit RS100 and precirol were formulated. Prior pre-formulation studies carried out on powder blend showed good flow properties.

Routine quality evaluations of the VHL-SR tablets were found within the acceptable range. The results of in-vitro drug release study indicated that the formulation containing Carbopol 71G (50 mg), Xanthan gum (75 mg) and MCC (50 mg) extended the release of the VHL. Formulation F15 was the optimized one which gave satisfactory release (95.2%) for 16 hr and with a similarity factor (f2) 68.46 as compare to other batch formulations. The formulation showed appreciable stability under accelerated conditions of temperature and humidity after 2 m. The methodology adopted was found to be successful to formulate VHL-SR release tablets.

References

1. Vyas S.P., Khar R.K. Controlled Drug Delivery: Concepts and Advances. 1st Ed. Vallabh Prakashan, Delhi, 2002.

2. Verma R.K., Garg S. Current Status of Drug Delivery Technologies and Future Directions. Pharma. Techno. 2001; 25(2):1-13.

3. Deasy P.B. Microencapsulation and Related Drug Process. Marcel Dekker Inc, New York, 1984.

4. Robinson J.R., Lee V.H. Controlled Drug Delivery: Fundamentals and Applications. Marcel Dekker 2nd Ed. New York, 1987.

5. Ritschel W.A. Biopharmaceutical and Pharmacokinetics Aspects in the Design of Controlled Release peroral Drug Delivery Systems. Ind. Pharm.1989; 15:1073-103.

6. Rao K.S., Jadhav S., Patil P., Ddattatraya D.U. Development And Evaluation Of Sustained Release Tablets Of Venlafaxine Hydrochloride, International Research Journal Of Pharmacy, 2(5),2011,261-270.

7. Doddayya H., Patil S.S., Kaledhele A., Udupi R.H., Reddy S.R., Kumar P. Effect of gum rosin and ethyl cellulose on in vitro release of venlafaxine hydrochloride from hydrophilic matrix tablets. Int. Pharm. Biol. Archiv. 2011; 2(3): 980-988.

8. Radhika P.R., Karanam D., Sivakumar T. Fabrication of sustained release matrix tablets of venlafaxine hydrochloride using eudragits. Int. Res. Ayur. Pharm. 2011; 2(4): 1386-1389.

9. Atul A. B, Prashant Z, A.V. Chandewar,S B Jaiswal, Designing And Evaluation Of Extended Release Tablet Of Venlafaxine Hydrochloride Using Hydrophobic Matrix. Der Pharmacia Lettre. 2010; 2(1): 329-335.

10. Phoke S.V., Sakarkar D.M., Mitkare S.S. Formulation and characterization of sustain release matrix tablets of venlafaxine hydrochloride by using natural polymers. Int. Pharm. Front. Res. 2012; 2(4): 14-26.

11. Thorat R., Patil P., Aage R., Puranik P., Salve V. Formulation development and evaluation of venlafaxine hydrochloride sustained release matrix tablet. Int. Pharm. Pharm Sci. 2013, 5(3): 757-765.

12. Raju G., Kumara Swamy S., Agaiah G.B. Formulation and evaluation of extended release matrix tablets of venlafaxine hydrochloride. J Adv. Pharm. Sci. 2012; 2(1):213-221.

13. OmPrakash B., Sav A., Gejage S., Amin P. Formulation development of venlafaxine hydrochloride extended release tablet and in vitro characteristics. Int. J. Pharm. Tech Res. 2012; 4(4): 1777-1784.

14. Bhutani S.B. Development and optimization of venlafaxine hydrochloride sustain release triple layer tablets adopting quality by design approach. Pharmacol. Pharm. 2013; 4: 9-16.

15. Gohel M.C., Soni, C.D., Nagori S.A., Sarvaiya K.G. Modulation of Venlafaxine Hydrochloride Release from Press Coated Matrix Tablets. Indian J. Pharm. Sci. 2008; 70(3): 292-297.

16. Bhalekar M.R., Madgulkar A.R., Sheladiya D.D., Kshirsagar S.J., Wable N.D., Desale S.S. Statistical Optimization of Sustained Release Venlafaxine HCL Wax Matrix Tablets. Indian J. Pharm. Sci. 2008; 70(3): 472-476.

17. Madgulkar A.R., Bhalekar M.R., Kohle V.J., Kenjale Y.D. Formulation and Optimization of Sustained Release Tablets of Venlafaxine Resinates Using Response Surface Methodology, Indian J. Pharm. Sci. 2009; 7(14): 387-394.

18. Sowmya C., Reddy Y. P., Kumar M. K., Raja M.S. Development And Validation Of spectrophotometric method for

the estimation of Venlafaxine In bulk and formulations, Int. J. Chem. Sci. 2011; 9(1): 52-58.

19. Prasad V., Senthil A., Mahalaxmi D., Chinnareddy P., Mohideen S. Development and evaluation of mucoadhesive buccal tablets of Venlafaxine HCl. Int. J. Biol. Pharm. Res. 2010; 1(2): 100-107.

20. Costa P., Lobo M.S. Modelling and Comparison of Dissolution Profiles. Euro. J. Pharma. Sci. 2001; 13:123–33.

21. Colombo P., Bettini R., Santi P., Peppas N.A. Swellable Matrices for Controlled Drug Delivery, Gel Layer Behavior, Mechanisms And Optimal Performance. Pharm Sci Tech Today 2000; 3:1-12.

22. Ritger P.L., Peppas N.A. A Simple Equation for Description of Solute Release II. Fickian and Anomalous Release from swellable Devices. J. Control. Rel. 1987; 5:37-42.

23. Hsu J.Y., Hsu M.Y., Liao C.C., Hsu H.C. On the Characteristics of the FDA's similarity factor for comparison of drug dissolution. J Food Drug Anal.1998, 553-558.

24. Nayak B.S., Nayak U.K., Patro B.K., Rout P.K. Design and evaluation of controlled release Bhara gum microcapsules of famotidine for oral use. Res. J Pharm. Tech. 2008; 1(4):433-437

25. Sabitha P., Ratna J.V., Reddy K.R. Design and evaluation of controlled release chitosan-calcium alginate microcapsules of anti-tubercular drugs for oral use. Int. J Chem. Tech. Res. 2010; 2(1):88-98.

26. Mastiholimath V.S., Dandagi P.M., Jain S.S., Gadad A.P., Kulkarni A.R. Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. Int. J Pharmceu. 2007; 328:49-56.

27. Shrivastava T., Upamanyu N., Mishra S., Sharma A., Raghuwanshi N. Release kinetic study of Lensoprazole Microcapsule. Int. J Pharm. Tech. Res 2012; 4(2):1-12.

28. Oishi T.S., Nimmi I., Islam S.M.A. Comparative in vitro bioequivalence analysis of some generic tablets of Atorvastatin, a BCS class II compound. BanglaDesh Pharm. J. 2011; 14(1): 61–66.

29. Ma M.C., Lin R.P., Liu J.P. Statistical evaluations of dissolution similarity. Statistica Sinica. 1999; 9: 1011–1027.

30. Demirturk E., Oner L. Evaluation of in vitro dissolution profile comparison methods of immediate release Gliclazide tablet formulations. J Facul. Pharm. 2005: 25(1):1–10.

31. Kaur J., Alex Joseph S., Gupta A., Singh Y., Kona S, Jain G. Development and Validation of Stability Indicating Method for Quantitative determination of Venlafaxine HCL in Extended Release Formulations Using High Performance Liquid Chromatography. J Pharm. Biol. Sci. 2010; 2 (1): 22-26.