ORAL DELIVERY OF VENLAFAXINE FROM CONTROLLED POROSITY OSMOTIC PUMP TABLET - FORMULATION AND IN VITRO EVALUATION

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Abstract

Controlled release tablets of venlafaxine to be taken at a dosing interval of 12 hours were formulated with venlafaxine hydrochloride (VFH) equivalent to 75 mg of venlafaxine base. Controlled Porosity osmotic pump (CPOP) based drug delivery system was selected for controlled release of venlafaxine. Target release profile, calculated from pharmacokinetic data, was selected and different variables were optimized to achieve the same.

The effect of different formulation variables, namely, relative amount of drug to osmogent, coat depth of semi permeable membrane, type of plasticizer and type and level of pore former on the in-vitro release was studied. Cellulose acetate (CA 398-10) was used as the semipermeable membrane. It was found that drug release rate increased with the amount of osmogent because of the increased water uptake, and hence increased driving force for drug release. VFH release was inversely proportional to the thickness of semipermeable membrane; however, directly related to the level of pore former in the membrane. This system was found to deliver VFH at a zero-order rate for 12 hours. Drug release from the developed formulations was free of pH and agitational intensity, but was dependent on the osmotic pressure of the release media. Results of scanning electron microscope studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane.

The in-vitro results of the developed formulations were compared with performance of standard marketed formulation of VFH. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. The superposition method was used to predict steady state plasma levels of VFH after administration of a test dose (75 mg) of optimized formulation.

Keywords: Venlafaxine; Controlled Porosity osmotic pump; Osmogent; Cellulose acetate membrane; Pore former

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1.
2. INTRODUCTION

Osmotically controlled oral drug delivery systems (OCODDS) make use of osmotic pressure as the source of energy for the controlled delivery of drugs. Drug release from these systems is not dependent on pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a great extent, and release character can be easily adjusted by optimizing the parameters of the drug delivery system [1–3, 26].

Venlafaxine is a distinctive antidepressant that differs structurally from other currently available antidepressants [4]. Venlafaxine and its active metabolite, o-desmethylvenlafaxine (ODV), inhibit the neuronal uptake of norepinephrine, serotonin and to a lesser extent dopamine [5,6] but have no monoamine oxidase inhibitory activity and a low affinity for brain muscarinic, cholinergic, histaminergic or α adrenergic receptors [7,8]. Hence, it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants. The steady state half lives of Venlafaxine and ODV are 5 and 11 hr, respectively, necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug [9].

Thus, there is a strong clinical require and market prospective for a dosage form that will deliver Venlafaxine in a controlled manner to a patient needing this therapy, thereby resulting in an improved patient compliance and conformity.

The present study was aimed towards the development of extended release formulations of venlafaxine based on osmotic technology. A theoretically designed zero-order delivery pattern was deigned to produce plasma level within the desired range [27]. The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core. The poorly water-soluble drugs do not create sufficient osmotic pressure and are delivered at low rates. To overcome this problem, other types of osmotic pumps for poorly water-soluble drug have been designed which are very complicated in design and difficult to optimize [10,11]. In contrast, highly water soluble drugs may create considerable osmotic pressures and may release the active drug at undesirable high rates. In some cases this problem may be solved by addition of a solubility-modulating agent to the core [12,13]. Venlafaxine is highly water soluble drug and hence solubility modulation was done. Different formulation variables were studied and optimized to achieve the desired release profile. The manufacturing procedure was standardized and the stability of the formulations evaluated after 3 months of storage at accelerated stability conditions.

3. MATERIALS:

Venlafaxine hydrochloride was a gift sample from Alembic Ltd. Baroda, India. Sodium chloride, tartaric acid, mannitol, and starch were purchased from Qualigens Fine Chemicals, Mumbai, India. PVP K30 and colloidal silicon dioxide were purchased from Signet chemical cooperation, Mumbai, India. Cellulose Acetate (CA 398-10) was a gift sample from Signet chemical cooperation Pvt. Ltd., Mumbai, India. PEG-400, PEG-4000, sorbitol, and glycerin were purchased from S.D. Fine Chem Limited, Mumbai, India. Isopropyl alcohol, Methanol and Acetone were purchased from Merck Limited, Mumbai, India. HPLC grade water was used for the HPLC analysis. All the other reagents used were of analytical grade.

4. METHODS:

Drug-Excipient Interaction Studies

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the preformulation stage during the development of a solid dosage form.

Infrared spectroscopy (FTIR). Infrared spectra of pure VFH, physical mixture of core tablets, placebo of core tablets, and coated tablets were recorded (Shimadzu, Model 8400S, Japan). All the discs were prepared in a KBr press. The samples pellets were scanned from 4500 cm^{-1} to 450 cm^{-1}.

Differential scanning calorimeter (DSC). The DSC thermograms of pure drug, core tablets, placebo of core tablets, and coated tablets were recorded. The samples were separately sealed in aluminium cells and set in DSC (Universal V4.2E TA Instruments). The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 50°C to 300°C.

Preparation of core tablets of VFH

All formulations were prepared by wet granulation method. All raw materials were sifted through 60 mesh. VFH powder was mixed with sodium chloride or mannitol and lactose in a mixer granulator for 10 minutes. The above mixture was passed through 30 mesh sieve. The dry blend was granulated with PVP K-30, dissolved in IPA. The wet blend was granulated and dried at 40-50 °C and sized through 20 mesh. To this mixture, colloidal silicon dioxide was added and granules were lubricated with magnesium stearate for 10 more minutes. The resulted granules were compressed into core tablets on 8 station single rotary compression machine (KMP-8, Cadmach Engg., Ahmedabad, India) with 8 mm round standard concave punches. The weight of each tablet was maintained within the range of 180 ± 5 mg and the drug loading was 75 mg/tablet. The composition of tablets was shown in Table 1.

Coating

Core tablets of VFH were coated in a conventional laboratory coating pan (Sehgal Industries Ltd., New Delhi) fitted with three baffles placed at angle of 120° each. The composition of coating solutions used for coating of core tablets is given in Table 2. Various components of coating solution were added to solvent mixture in sequential manner. Coating solution was prepared by dissolving accurately weighed quantities of polymer, pore formers and plasticizer in the solvent (ethanol and acetone 1:9 mixture) using a stirrer. The component added first was allowed to dissolve before next component was added. Coating process was done on a batch of 250 tablets. Pan speed was set at 22 rpm and inlet hot air temperature was set at 45°C. The manual coating procedure based on intermittent spraying and coating was used with spray rate of 2ml/min followed by 4 ml/min. Coat weight and thickness were controlled by the volume of coating solution consumed in coating process[14]. After attaining the desired coat thickness, the tablets were dried in an oven at 60°C for 3 to 4 hours followed by drying at room temperature for 8 to 10 hours. The prepared osmotic pump tablets were kept in a desiccator for future experiments.

Evaluation of Developed Formulation

Bulk and tap density of the powdered blend was determined using the USP method II [15] and the compressibility index and Hausner ratio were calculated.

Evaluation of Core and Coated Tablets

The core and coated tablets were evaluated for weight variation. Thickness and diameter of core and coated tablets were measured using screw gauze (Campbell Electronics Mumbai, India). Hardness of randomly selected tablets was tested using hardness tester (Monsanto hardness tester, Campbell Electronics Mumbai, India). Friability of core tablets was carried out on Electrolab friability tester (Electrolab,

Mumbai, India) using 20 accurately weighed tablets.

Drug Content Uniformity

Accurately weighed 20 tablets (of all batches) were dissolved in 500 ml of distilled water. The samples were sonicated for 30 min. and filtered through 0.45µm nylon membrane filter. The filtered samples, after appropriate dilution were analyzed at 274 nm using UV/Visible spectrophotometer (Shimadzu, 1601 and 1800, Japan).

In-Vitro Drug Release Study

The developed formulations (n=3) of VFH were subjected to release studies using USP dissolution apparatus type I (Electrolab, TDT 06T, Mumbai, India) at 75 rpm. Dissolution media used was simulated intestinal fluid (SIF without enzymes, pH 6.8, 900ml) maintained at 37± 0.5 °C. The samples (5 ml) were withdrawn at different time intervals and replaced with equivalent prewarmed (37± 0.5 °C) volume of fresh medium. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using UV/Visible spectrophotometer at 274 nm. After analyzing the drug content in the dissolution samples, correction was made for the volume replacement and the graph of cumulative percent of drug release versus time was plotted.

HPLC Analysis

Chromatographic separation of Venlafaxine hydrochloride was performed on a Shimadzu SDP-10 HPLC system using Kromasil C_{18} column (25 cm × 4.6 mm × 5µm particle size; Shimadzu, Kyoto, Japan). Mobile phase used was filtered mixture of buffer solution (1.74 gm of potassium dihydrogen phosphate was dissolved in HPLC water and volume was made up to 1000 ml and pH was adjusted to 7.0 with 10% orthophosphoric acid) and and acetonitrile prepared in the ratio of 35:65, with pH 6.8. Temperature of the column was maintained at 45°C. Injected volume was 10µl and standard solution and dissolution samples were analyzed at 227 nm using a UV detector.

Statistical Analysis

Experimental results were expressed as mean ± S.D. values. Release profiles of various batches were compared using model independent pair wise approach, which include the calculation of 'difference factor' f_1 and 'similarity factor' f_2. The two release profiles were considered to be similar if f_1 value was lower than 15 (between 0 to15) and f_2 value was more than 50 (between 50 to100). Release profiles were also compared using mean dissolution time or MDT which was calculated using following equation [16]:

$$MDT = \frac{\sum_{j=1}^{n} t_j \Delta Mj}{\sum_{j=1}^{n} \Delta Mj} \quad (1)$$

where, j is the sample number, n is the number of dissolution sample times, t_j is the time at mid point between t_j and $t_{(j=1)}$, and ΔMj is the additional amount of drug dissolve between t_j and $t_{(j=1)}$. One way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations. Difference was considered statistically significant at $p<0.05$. In this study, mean dissolution time for 50 % drug release ($MDT_{50\%}$) was used for comparison of release profiles from different batches.

Scanning Electron Microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by

scanning electron microscope (JSM-6390 LV SEM, Jeol Japan). Membranes were dried at 45°C for 12 hrs and stored between sheets of wax paper in desiccator until examination.

Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, in vitro release studies were conducted in media of different pH. The release media was SGF (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8). Samples were analyzed by UV/Visible spectrophotometer.

Effect of Agitational Intensity

In order to study the effect of agitational intensity of the release media, release studies were performed in dissolution apparatus at various rotational speeds. USP-I (rotating basket) type dissolution apparatus with rotational speeds of 75, 100, and 150 rpm was used. Degassed SIF (without enzymes) was used as dissolution media (pre-equilibrated to 37°C ± 1°C). Samples were analyzed spectrophotometrically after filtration through 0.45 µm nylon membrane filters.

Effect of Osmotic Pressure

To confirm the major mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to 37°C ± 1°C), sodium chloride (osmotically effective solute) was added in SIF (without enzymes). Release studies were performed in 900 mL of media using USP-I dissolution apparatus (75 rpm). Samples were analyzed spectrophotometrically after filtration through 0.45 µm nylon membrane filters.

Burst Strength

Burst strength of the exhausted shells, after 8 hr of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength was determined as the force required to break/rupture the shells after dissolution studies. The texture analyzer (TAX T2i, Stable Micro systems, England) with a 5 kg load cell and 25 mm aluminium cylindrical probe was utilized for this purpose. Test speed of 0.8 mm/sec was selected and the distance moved was set at 2 mm.

Kinetics and Mechanism of Drug Release

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR) and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model.

Accelerated Stability Studies

Optimized formulations of VFH were packed in blisters (10 tablets in one strip) of 0.25mm amber PVC with 0.05mm lidding aluminum foil. The packed formulations were stored in ICH certified stability chambers (NSW-175, Narang Scientific work, New Delhi, India) maintained at 40 °C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug content, hardness, burst strength and release studies. The withdrawn samples, after filtration through 0.45 µm nylon membrane filters, were analyzed using HPLC method

Prediction of In-Vivo Performance

Using the known pharmacokinetic properties of VFH (Table 3) and various drug release parameters (R^0 and t_{Del}), which were calculated from in vitro release data, steady-state plasma levels of drug were predicted by the method of superposition[17]. It was assumed that after

the administration of a test dose of formulation, the drug would be released at a release rate (R^0) for a period of time (t_{Del}), shorter than the selected dosing interval (Ƭ). Time of delivery, t_{Del}, is the time taken to deliver 90% of the total drug within a selected dosing interval (Ƭ = 12 hr). The predicted plasma levels of developed CPOP were compared with those of desired level by calculating the percent-predicted error (% PD) in C_{max} and AUC $_{0-Ƭ}$. Bioequivalence was anticipated if the average % PD was less than 15% for C_{max} and AUC $_{0-Ƭ}$ [18,19]. The % PD was calculated using the following equation:

$$\%\ PD = \frac{\text{Predicted value} - \text{Reference value}}{\text{Reference value}} \times 100 \quad (2)$$

5. RESULTS AND DISCUSSION:

Drug-Excipient Interaction Studies

The IR spectrum of pure VFH showed the predominant peak at 3350 cm^{-1} (-OH str. free hydroxyl group), 2937 cm^{-1} (due to C-H stretching of methyl group), 1513 cm^{-1} (phenyl group, C-C str.), 1246 cm^{-1} (aryl alkyl ether) and 1176 cm^{-1} (3° aliphatic amine, C-N str.). IR spectra of pure VFH, placebo blend of VFH, core blend of VFH tablets and VFH with cellulose acetate (CA 398-10), revealed that both characteristic bands of the drug and excipients were present in all the spectra (Fig. 1) and no new bands or shifts in characteristics peaks appeared in any sample, indicating absence of any interaction between the drug and excipients.

Figure 2 (Fig. 2) depicts the DSC thermograms of atenolol and the formulations. No changes in the endotherms were observed as the drug exhibited a sharp melting endotherm in the core and coated formulation. From the DSC thermograms it was clear that no specific interaction between the drug and excipients used in the present formulation.

Desired Drug Release Profile

Using the different pharmacokinetic parameters of VFH (Table 3), the dose needed to provide controlled delivery of TRH can be calculated by the following equation [20]:

$$D_o = Cp \times T \times Cl_T \quad (3)$$

where, D_o is the dose, Cp is the therapeutic drug plasma level, Cl_T is total clearance and T is the dosing interval. Therapeutic range for VFH is reported to be between 0.025 - 0.40 µg/ml [21] and the desired steady state concentration of VFH for a 75 mg dose is 0.065 µg/ml. Taking the steady state concentration as the desired therapeutic plasma level and the dosing interval of 12 h, the following values were proposed: (i) Sustaining dose 75 mg, (ii) zero-order release rate 6.0 mg/hr and (iii) dosing interval 12 h. By plotting the cumulative zero-order release (%) (y) vs. time (x), the desired release profile was generated and used as the target release profile for developed formulations.

Drug Content and Physical Evaluation

Compressibility index of powder blend calculated for all batches was found to be less than 15%. The assay of drug in various formulations varied between 98.6% and 103.5% (mean 101.05%). Core tablet weights varied between 172 mg and 184 mg (mean 178 mg), thickness of the core tablets was found to be in the range of 3.79 and 3.83 mm (mean 3.81 mm). The hardness of core tablets was found to be between 6.1 and 9.0 kg cm^2 (mean 7.5 kg cm^2), while the friability of prepared core tablets ranged between 0.12% and 0.26% (mean 0.19%). Thus, all the physical

parameters of the compressed matrices were practically within limits.

Effect of Ratio of Drug to Osmogent

To optimize the amount of osmogent to be used in the core formulations and to study the effect of drug to osmogent ratio, core formulations were prepared as shown in Table 1,. Sodium chloride and mannitol were used as osmotic agent. All the core formulations were coated with same composition containing 15% w/w (of cellulose acetate) of sorbitol. The % weight gain of all the coated formulations was 5±0.20%. The developed formulations (n=3) of VFH were subjected to release studies using USP type 1 dissolution apparatus at 75rpm. Dissolution media used was simulated intestinal fluid (without enzymes, pH 6.8, 900ml) maintained at 37±0.5°C. The samples (5ml) were withdrawn at different time intervals and replaced with equivalent prewarmed (37±0.5°C) volume of fresh medium. The withdrawn samples, after filtration and dilution were analyzed spectrophotometrically at 274 nm. Release profile from these formulations is shown in figure 3 (Fig. 3). It is clear that osmogent enhances the release of drug and had a direct effect on drug release. Formulation VFH1 was devoid of any osmogent in the core, showed 20.37% drug release after 8 hours. The use of osmogent enhanced the release which is due to the increased water uptake and hence increased driving force for drug release. The drug release after 8 hours for VFH2, VFH3, VFH4 and VFH5 (sodium chloride as osmogent) was 52.16, 69.26, 78.32 and 86.14% respectively and drug release after 8 hours for VFH6 and VFH7 (mannitol as osmogent) was 41.12%, and 50.37% respectively. From the comparative release profiles it was concluded that release of VFH form batch VFH3 is more controlled with highest zero-order coefficient of determination value (R^2 = 0.993) than other batches. Hence formulation VFH3 was chosen for further experimental studies.

Effect of coat thickness on drug release

To study the effect of coat thickness of SPM on drug release, release profiles of batch VFH3A1 (3% w/v coating solution with around 100 µm coat thickness), batch VFH3A2 (4% w/v coating solution with around 200µm coat thickness) and batch VFH3A3 (5% w/v coating solution with around 350 µm coat thickness) were studied. Release profiles from these formulations are shown in figure 4 (Fig. 4). The $MDT_{50\%}$ value between different batches (2 hr 20 min., 3 hr 3 min. and 3 hr 45 min. for formulations with coat thickness of 100 µm, 200 µm and 350 µm) were found to be statistically significant ($P < 0.05$).

Effect of type of plasticizer on drug release

To study the importance of type of plasticizer on VFH release, batch VFH3B1 was coated with SPM composition without plasticizer and batch VFH3B2 was coated with SPM containing PEG-400 as plasticizer (at level of 15% w/w of cellulose acetate) and batch VFH3B3, with dibutyl phthalate (at same level) as plasticizer. Release profiles from these formulations are shown in figure 4 (Fig. 4). It is observed that PEG-400 increases whereas dibutyl phthalate decreases the rate and extent of VFH release. The $MDT_{50\%}$ value between different batches ($MDT_{50\%}$ not achieved for batch VFH3B1, 3 hr 3 min. for batch VFH3B2 and 3 hr 54 min. for batch VFH3B3) were found to be statistically significant ($P < 0.05$).

Effect of type of pore former on drug release

To study the effect of type of pore former, formulations were prepared by coating core tablets of VFH with coating compositions containing different pore formers Sorbitol, Glycerol, PEG-4000 and

Tween 80. The pore formers were chosen from highly soluble polymers with different physicochemical properties i.e. Sorbitol (Saccharide), Glycerol (Trihydric Alcohol), PEG-4000 (Plasticizer) and Tween 80 (Surfactant). Release profiles from these formulations are shown in figure 4 (Fig. 4). $MDT_{50\%}$ for VFH CPOP tablets was found to be 3 hr 3 min., 3 hr 34 min., 4 hr 15 min. and 2 hr 35 min. for formulations containing Sorbitol (VFH3C1), Glycerol (VFH3C2), PEG-4000 (VFH3C3) and Tween 80 (VFH3C4) respectively as pore former. In addition to release, type of pore former also affect burst strength of the exhausted shells and this parameter should also be taken into consideration while selecting the pore former. The drug release and the burst strength were satisfactory with formulations containing sorbitol as the pore former. This pore former was selected for further studies.

Effect of concentration of pore former on drug release

To study the effect of level of pore former (sorbitol), core tablets were coated with coating compositions containing 0, 7.5, 15 and 20% (w/w of total solids) of sorbitol. It was found that drug release increases with the level of sorbitol. Release profiles from these formulations are shown in Fig. 4. At a low concentration of pore former, drug release was mainly caused by osmosis and with higher concentration of pore former, the diffusion component increases. At levels up to 7.5% (w/w) of pore former, numbers of pores are not sufficient to contribute to significant drug release. On the other hand, membranes that initially contained 15% (w/w) of pore former the membrane become more porous after coming in contact with water.

Effect of concentration of pore former on burst strength

Another parameter affected by the level of pore former was burst strength of the exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane (Fig. 5). Since, satisfactory drug release and adequate burst strength were obtained in case of formulations with 15% pore level. This formulation was selected as the "optimized" formulation and used for further evaluation.

Performance Evaluation of Optimized Formulation

Comparative evaluation with marketed extended release tablets

To evaluate the performance of optimized formulation, release profiles of batch VFH3D3 was compared with release profile of marketed extended release 75 mg formulation (VENTAB XL 75) of VFH and with theoretically desired release profile (Fig.6). Drug release from batch VFH3D3 was found to be closest to the desired release profile. The f1 and f2 values for batch VFH3D3 were 3.12 and 90.56, respectively, taking the desired release profile as reference, indicating no significant difference between batch VFH3D3 and the theoretically desired release profile.

Scanning Electron Microscopy

Cellulose acetate (CA) membranes of optimized formulation, (Batch VFH3D3), obtained before and after dissolution were studied by SEM. Membranes obtained before dissolution clearly showed nonporous region. After 8-hour dissolution, the membrane clearly showed pores in range of 5 to 10 μm (Fig. 7) owing to dissolution of sorbitol. The leaching of sorbitol from the membrane leads to formation of pores, and thus the release of drug takes place.

Effect of pH

The optimized formulation Batch VFH3D3, was subjected to in vitro release studies in buffers with different pH. As can be seen from figure 8 (Fig. 8), there is no

significant difference in the release profile, demonstrating that the developed formulation shows pH-independent release.

Effect of Agitation Intensity

The release profile of VFH from the optimized formulation Batch VFH3D3 was independent of the agitational intensity of the release media (Fig. 9). The difference factor (f_1) and similarity factor (f_2) values were found to be 2.03 and 92.12 (for 75 and 100 rpm), 1.57 and 95.21 (for 100 and 150 rpm), and 3.47 and 93.02 (for 75 and 150 rpm). Therefore, the formulations can be expected to show a release profile, fairly independent of the hydrodynamic conditions of the body.

Effect of Osmotic Pressure

The effect of osmotic pressure on the optimized formulation was studied in media of different osmotic pressure. The drug release rate decreased with increase in osmotic pressure in the media; however, the lag time was prolonged. The drug release profiles with varying osmotic pressure are shown in figure 10 (Fig. 10), and it is evident that the drug release from the formulation decreased as the osmotic pressure of the media increased. This finding confirms that the mechanism of drug release is by the osmotic pressure.

KINETICS AND MECHANISM OF DRUG RELEASE

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR), best goodness-of-fit test (R^2) and higher correlation coefficient were taken as criteria for selecting the most appropriate model. Drug release from optimized formulations (Batch VFH3D3) fitted well into zero-order kinetics (Table 4) confirming that the release from formulation is close to desired release.

ACCELERATED STABILITY STUDY

The stored formulations of batch VFH3D3 were found to be stable in terms of drug content and dissolution stability (Table 5). In all the cases, the burst strength was higher than the reported values of mechanical destructive forces in the GIT ensuring the formulations to be intact in GIT without any incidence of dose dumping even after storage. The f_1 and f_2 value were calculated with initial analysis was taken as a reference and 1 month, 2 month and 3 month data as test.

IN-VIVO PREDICTION

Method of superposition was used to predict steady state plasma levels of VFH after administration of a test dose (75 mg) of optimized formulation (Batch-VFH3D3). Since osmotic pumps are reported to exhibit a significant in vitro/in vivo correlation, predicted data of steady-state plasma levels from drug release studies can be used for comparison with the desired plasma levels. The desired steady-state plasma levels of VFH were predicted from a theoretically designed zero order delivery system. Prediction of steady-state levels of VFH after administration of a test dose of optimized formulation showed that plasma levels are between 250 ng/ml to 400 ng/ml. Figure 11 (Fig. 11) shows predicted steady-state plasma levels after administration of a test dose of Batch-VFH3D3 formulation in comparison to the desired steady state plasma levels. It is clearly evident from the figure that the predicted steady state plasma levels are very close to the desired levels. The predicted Css max and AUC_{0-t} after administration of optimized formulations of VFH, in comparison with the desired ones is listed in Table 6. The % PD of the steady-state parameters of optimized formulations was calculated taking the data of desired profile as the

reference. The absolute % PD was found to be less than 15%, ensuring that the optimized formulations will produce plasma levels close to the desired ones. Thus, it can be concluded that the developed optimized formulation (batch-VFH3D3) will produce plasma levels well within the therapeutic range. Since osmotic pumps are reported to exhibit a good in vitro/in vivo correlation, based on in vivo performance prediction, the developed formulations can be expected to perform similar in vivo.

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There are no conflicts of interest.

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Table 1: Formula for different batches of core formulations of VFH

S.No	Ingredients (mg/tablet)	VFH1	VFH2	VFH3	VFH4	VFH5	VFH6	VFH7
1.	Venlafaxine	84.86	84.86	84.86	84.86	84.86	84.86	84.86

	hydrochloride*							
2.	Sodium chloride	_	15	30	45	60	_	_
3.	Mannitol	_	_	_	_	_	30	60
4.	Lactose	85.14	70.14	55.15	40.14	25.14	55.15	25.14
5.	PVP K-30	7	7	7	7	7	7	7
6.	Magnesium stearate	2	2	2	2	2	2	2
7.	CSD	1	1	1	1	1	1	1
	Total	**180**	**180**	**180**	**180**	**180**	**180**	**180**

***** Venlafaxine hydrochloride equivalent to 75 mg Venlafaxine
PVP- polyvinyl pyrrolidone K30, CSD-Colloidal silicon dioxide

Table 2: Composition of various coating solutions of CPOP tablets of VFH

Ingredients	**Coating code**												
	A1	**A2***	**A3**	**B1***	**B2***	**B3***	**C1***	**C2***	**C3***	**C4***	**D1***	**D2***	**D3***	**D4***
Cellulose Acetate 398-10	2.10 gm	2.80 gm	3.50 gm	3.4 gm	2.8 gm	2.8 gm	2.8 gm	2.8 gm	2.8 gm	2.8 gm	3.4 gm	3.1 gm	2.8 gm	2.6 gm
PEG-400	0.45 gm	0.60 gm	0.75 gm	_	0.6 gm	_	0.6 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm
Dibutyl phthalate	-	-	-	_	_	0.6 gm	-	-	-	-	-	-	-	-
Sorbitol	0.45 gm	0.60 gm	0.75 gm	0.6 gm	0.6 gm	0.6 gm	0.6 gm	_	_	_	_	0.3 gm	0.6 gm	0.8 gm
Glycerol	-	-	-	-	-	-	_	0.6 gm	_	_	-	-	-	-
PEG-4000	-	-	-	-	-	-	_	_	0.6 gm	_	-	-	-	-
Tween 80	-	-	-	-	-	-	_	_	_	0.6 gm	-	-	-	-
Ethanol	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Acetone	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml

A1 = 3% w/v total solids in coating solution
A3 = 5% w/v total solids in coating solution
***** = 4% w/v total solids in coating solution

Table 3: Various pharmacokinetic parameters of Venlafaxine

Pharmacokinetic parameters	**Value**	**Reference(s)**
Bioavailability (f)	45%	[22-25]
Elimination half life ($t_{1/2}$)	4.9 hr	[22-25]
Terminal deposition rate constant (K_{el})	0.06 h^{-1}	[22]
Apparent volume of distribution (V_d)	7.5 liters/kg	[22-25]
Maximum safe conc. (MSC)	0.4 µg/ml	[21]
Minimum effective conc. (MEC)	0.025 µg/ml	[21]
Clearance total (Cl_T)	22 ml/min/kg	[22-25]

Table 4: Mechanism of drug release of optimized formulation (Batch No.VFH3D3) according to various mathematical models

Models	**R^2**	**R**	**intercept**	**k**	**SSR**
Zero order	0.999	0.999	-0.888	6.435	5.906
First order	0.969	0.984	2.044	-0.0617	132.142
Higuchi model	0.963	0.981	-23.329	30.290	152.476

R^2: goodness of fit; **r:** correlation coefficient, **SSR**: sum of squares of residuals, **k:** release rate constant for respective models (k_0 in mg/h, k_1 in h^{-1} and k_h in % $h^{1/2}$ for zero-order, first order, and Higuchi rate equations respectively).

Table 5: Evaluation of batch VFH3D3 (optimized formulation) for various parameters during 3 months of storage at 40°C and 75% RH [mean ± S.D. (n=3)]

Parameter	**Initial**	**1 month**	**2 month**	**3 month**
Drug content (%)	98.61 ±1.42	98.12±1.52	98.63±1.25	98.01±1.72
Hardness (kg/cm^2)	7	7	8	8
Burst strength (kg)	416±21	426±24	443±28	449±30
f_1	-----	2.1	3.5	4.1
f_2	-----	94.7	93.3	92.3
MDT $_{50\%}$ (hrs.)	3.061	3.110	3.155	3.172

Table 6: Predicted In-Vivo performance of the developed optimized CPOP of VFH

Product	**Predicted $C_{ss\ max}$ (ng/ml)**	**% PD**	**Predicted AUC_{0-t} (ng hr/ml)**	**% PD**
Desired [a]	606	---	109	---
Batch VFH3D3 [b]	580	- 4.29	107	- 1.83

[a] Predicted from desired zero-order delivery profile (Dose = 75mg, R^0= 6.6mg/hr, and t_{Del} 7.63 hr).
[b] Predicted from drug release study (Dose = 75mg, R^0= 6.42mg/hr, and t_{Del} 8.00 hr).

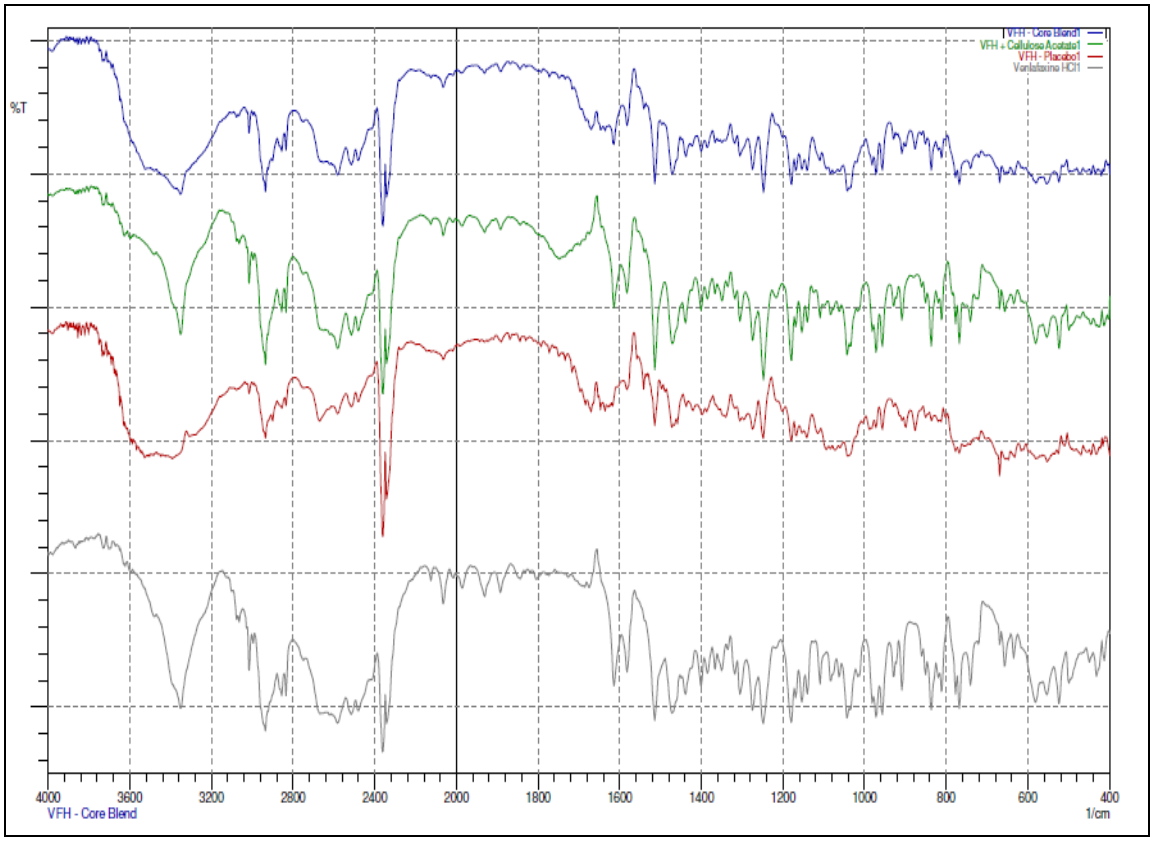

Fig. 1: FT-IR spectra of VFH, placebo blend, VFH with cellulose acetate and core blend of VFH.

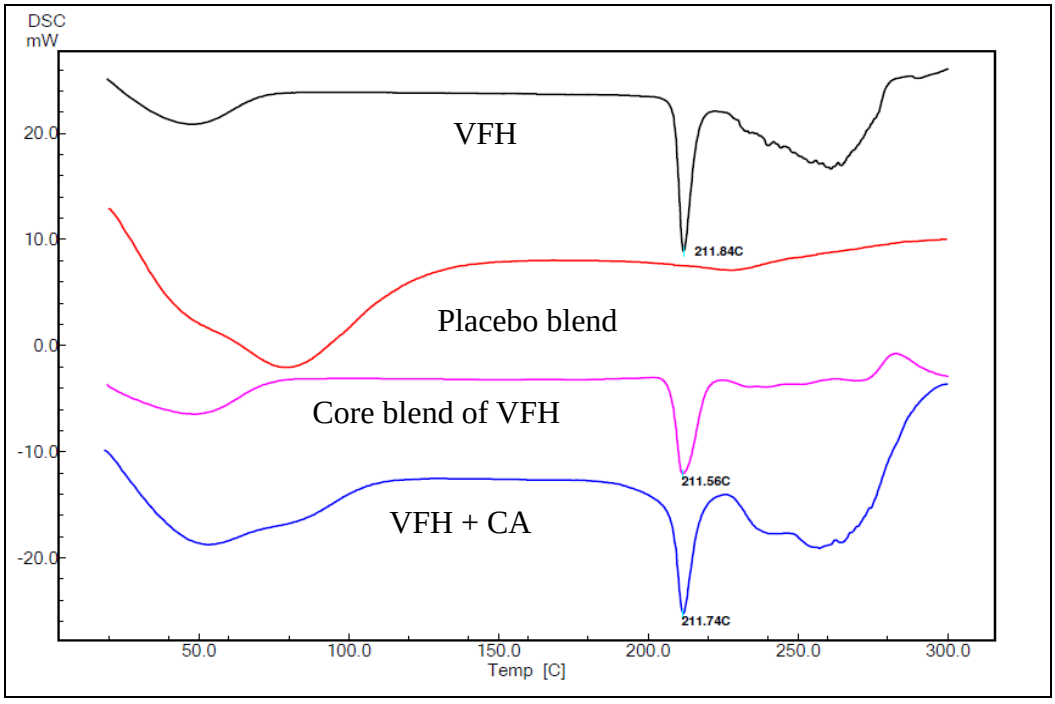

Fig. 2: DSC thermograms of VFH, placebo blend of VFH, core blend of VFH

and VFH+CA

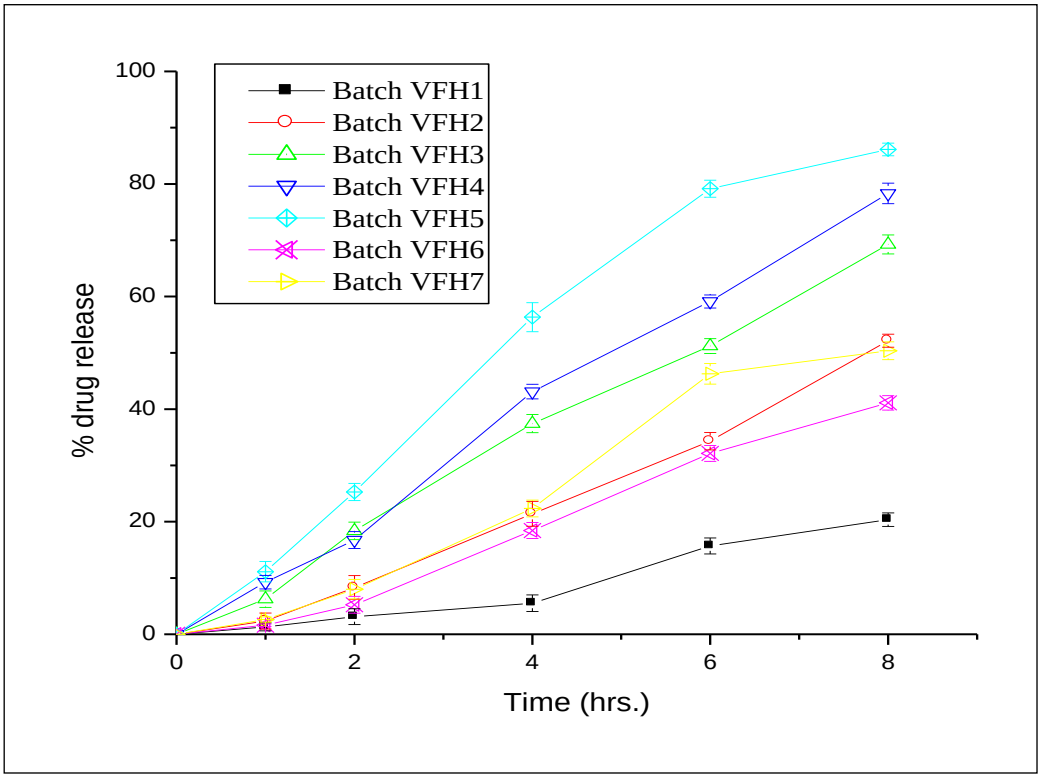

Fig. 3: Effect of osmogent on in-vitro percent release of VFH CPOP tablets. Bars represent ± S.D. (n=3)

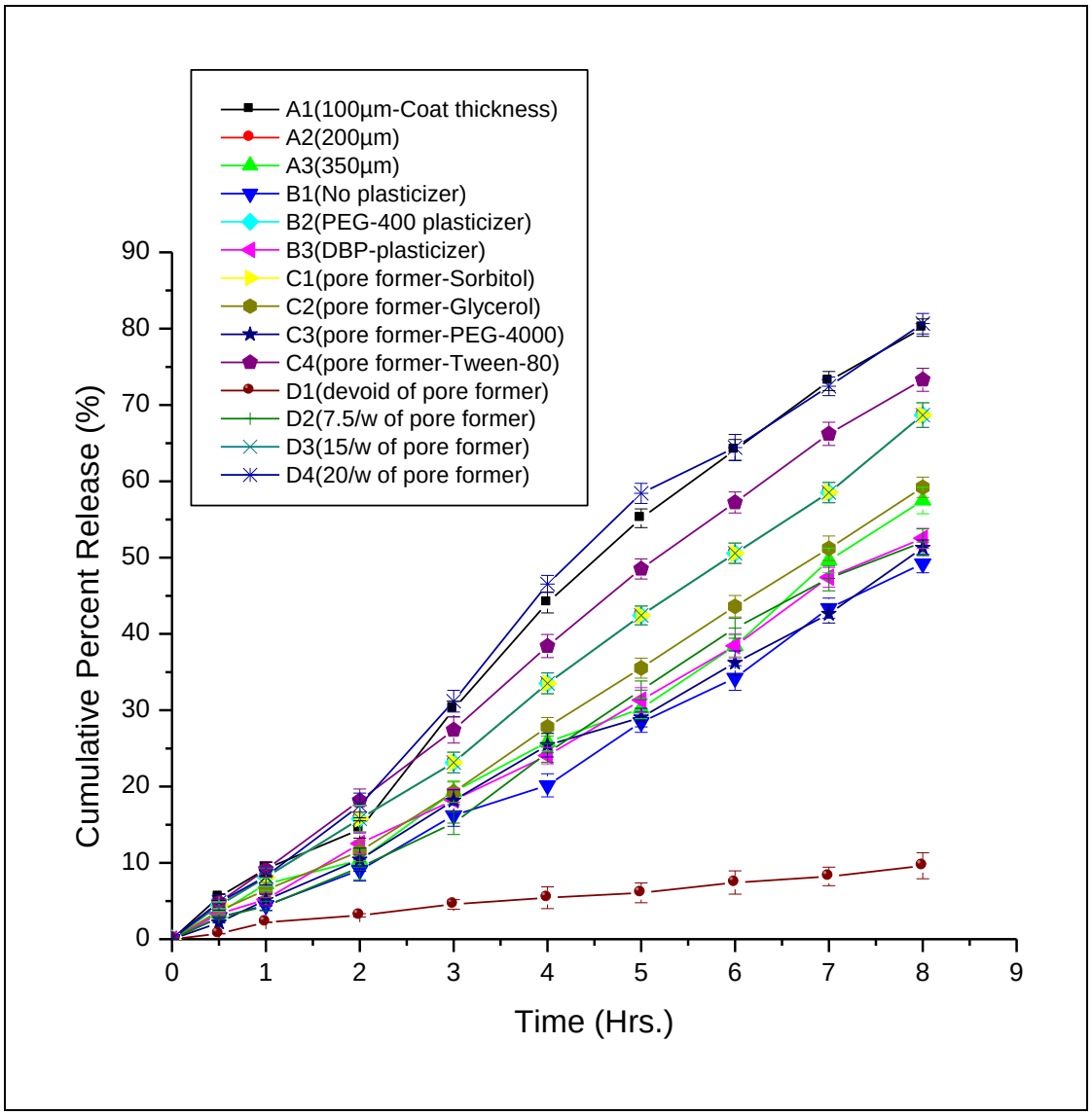

Fig. 4: Effect of various coating parameters on in-vitro release of VFH CPOP tablets. Bars represent ± S.D. (n=3)

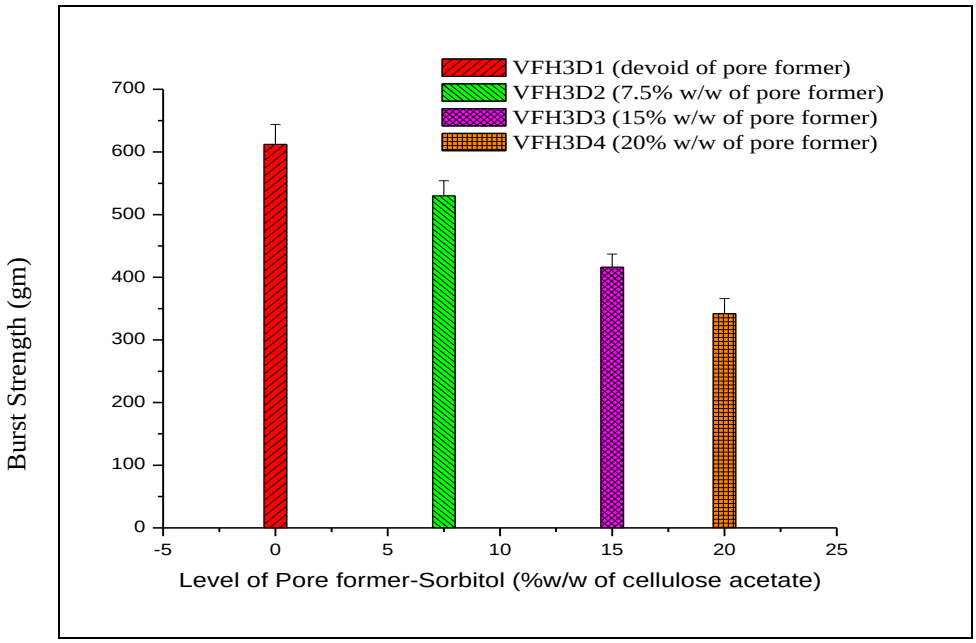

Fig. 5: Bar diagram showing the effect of concentration of pore former on burst strength of SPM membrane. Bars represent ± S.D. (n=3)

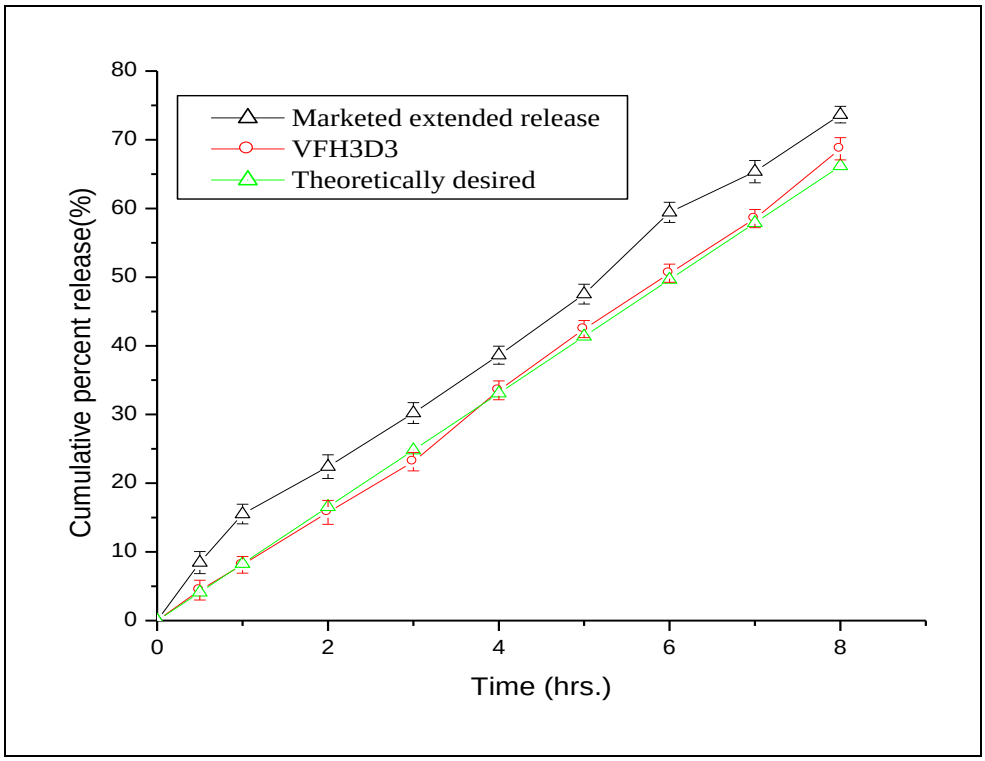

Fig.6: Release profile of optimized formulation of VFH CPOP tablet (VFH3D3) in comparison to marketed formulation and theoretically desired release profile (target). Bars represent ± S.D. (n=3)

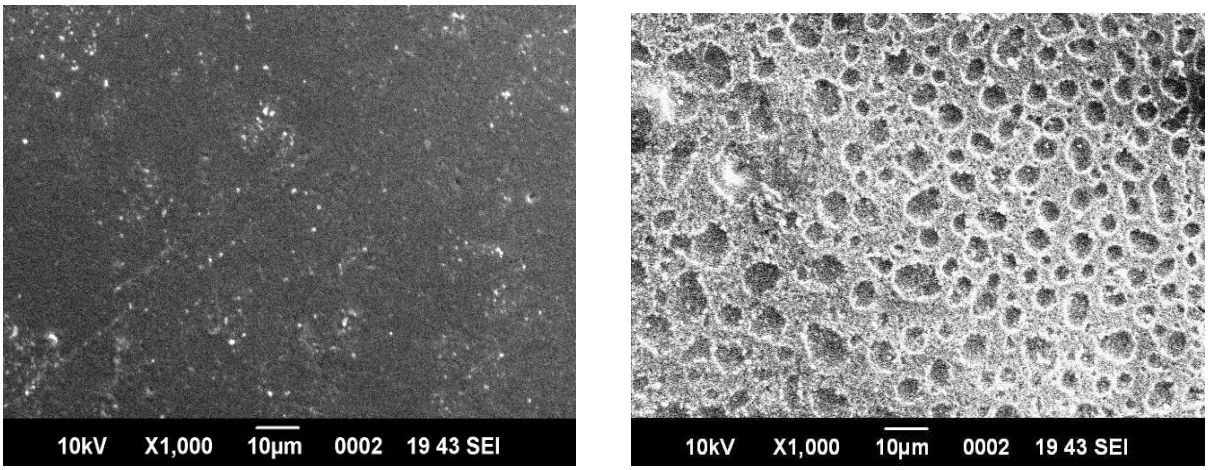

Fig. 7: Scanning electron microphotographs of membrane structure of optimized formulation before and after dissolution studies.

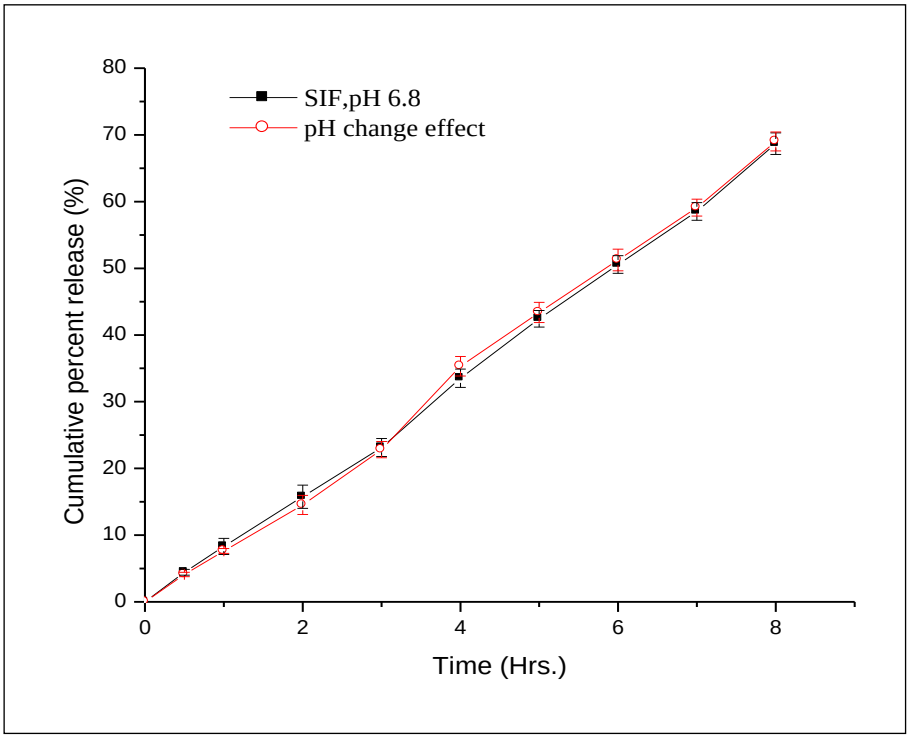

Fig.8: Release profiles showing the effect of pH on VFH release from optimized formulation (batch VFH3D3). Bars represent ± S.D. (n=3)

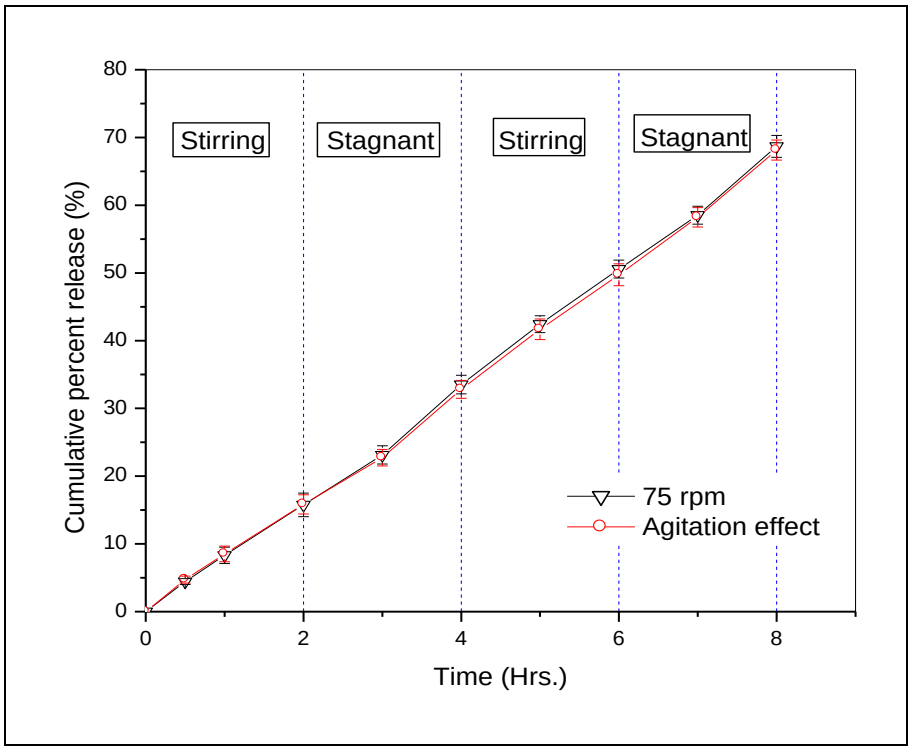

Fig.9: Release profiles showing the effect of agitation intensity of the release media on VFH release (batch VFH3D3). Bars represent ± S.D. (n=3)

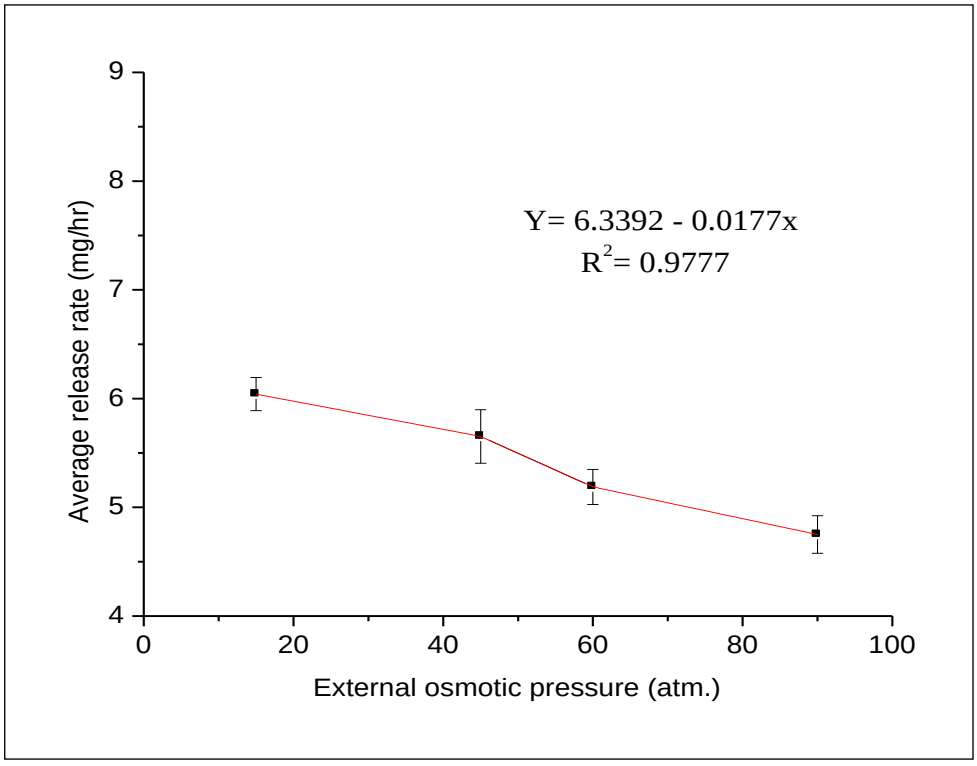

Fig.10: Linear relationship between the release rate and external osmotic pressure. Bars represent ± S.D. (n=3)

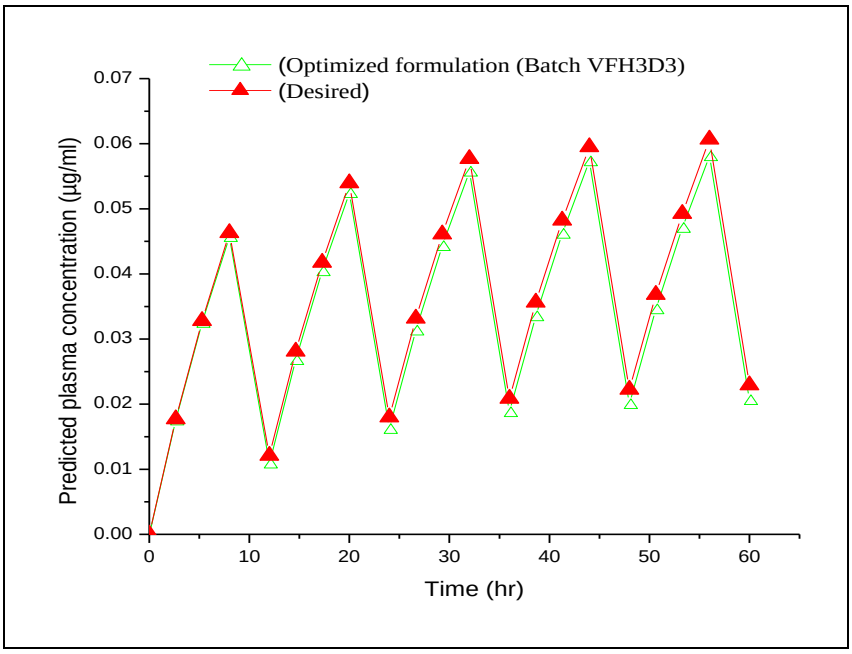

Fig.11: Predicted steady-state plasma levels of VFH following administration of test dose (75 mg VF) of optimized formulation (batch VFH3D3) in comparison with the desired profile.

Table and **Figure** Titles and Legends

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