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FORMULATION DEVELOPMENT AND IN-VITRO EVALUATION OF BILAYER TABLET OF ANTI-PSYCHOTIC DRUG WITH CHRONOPHARMACOKINETIC ASPECTS

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ABSTRACT

Depression is a common illness worldwide, with more than 264 million people affected. Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Venlafaxine is a serotonin reuptake inhibitor and is widely used in the treatment of depression. Venlafaxine has better tolerability than tricyclic antidepressants. Depression is strongly associated with circadian rhythm. Hence, the present investigation was concluded with an attempt to design and optimize a bi-layer tablet of Venlafaxine HCl to combat drug concentration fluctuation by circadian rhythm. The present research aimed to prepare a bi- layer tablet using a direct compression method using polymers HPMC K-4 and HPMC K-15. An instant release layer and matrix tablet were prepared and from the results of the evaluation, a bi- layer tablet was prepared. Further development of bilayer tablet was made by using a combination of both the polymers. All final formulations were evaluated for physical appearance, flow properties, hardness, friability, weight variation, drug content, thickness, and in-vitro drug release. Release kinetics of optimized formulation (F6) was studied and results suggested that formulation shows significant improvement over a conventional tablet. The study concluded that Venlafaxine HCl bi-layer tablet can effectively

combat drug fluctuations due to circadian rhythm and can be very effective in the treatment of depression.

KEYWORDS: Bi-layer tablet, Depression, circadian rhythm, Venlafaxine HCl, HPMC K-4, HPMC K-15 & in-vitro drug release.

1. INTRODUCTION

As per who — Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, and political belief, economic or social condition. The health of all peoples is fundamental to the attainment of peace and security and is dependent upon the fullest cooperation of individuals and States. The achievement of any State in the promotion and protection of health is of value to all. As the Coronavirus pandemic rapidly sweeps across the world, it is inducing a considerable degree of fear, worry, and concern in the population at large and among certain groups in particular, such as older adults, care providers, and people with underlying health conditions. The COVID-19 pandemic has disrupted or halted critical mental health services in 93% of countries worldwide while the demand for mental health is increasing, according to a new WHO survey. Depression is a common illness worldwide, with more than 264 million people affected. Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Although there are known, effective treatments for mental disorders, between 76% and 85% of people in low- and middle-income countries receive no treatment for their disorder. Barriers to effective care include a lack of resources, lack of trained healthcare providers, and social stigma associated with mental disorders. Another barrier to effective care is inaccurate assessment. Depression results from a complex interaction of social, psychological, and biological factors. People who have gone through adverse life events (unemployment, bereavement, psychological trauma) are more likely to develop depression. Depression can, in turn, lead to more stress and dysfunction and worsen the affected person's life situation and depression itself.

Recent findings have substantially increased our understanding of the pathophysiology of depression. There has been a correspondingly significant increase in our understanding of the efficacy and tolerability of currently available treatments. Despite our increased understanding of both its pathophysiology and treatment, depression remains highly

prevalent, accounting for more disability than any other disorder worldwide. It is the most significant risk factor for suicide, a leading cause of death worldwide, especially in adolescents, young adults, and elderly individuals. Indeed, suicide is the third leading cause of death in children and adolescents, and childhood depression and bipolar disorder are not uncommon, yet quite understudied. Depression is also an important risk factor both for the development of cardiovascular disease including myocardial infarction and congestive heart failure and for the poor response to treatment in these patients.

Depression in one or other of its many forms must surely be one of the most common problems encountered in the practice of medicine. During this period of rapidly advancing knowledge, the elucidation of factors involved in depression has proceeded along three main lines of endeavor.

- Intensive scrutiny of the psychodynamic mechanisms involved in the precipitation and continuance of depressive attacks.
- Study of the "organic factors which may initiate, underlie, or accompany the illness.
- Development of effective measures of treatment.

Antidepressants work by balancing brain neurotransmitters level to ease depression. Generally speaking, it takes about 2 weeks for the drugs to start working and about 6-9 months for the whole therapy or depends on the severity of illness as some people will need to take them longer. There are many antidepressant drugs available. The key role is played by the time that might be required for a particular outcome of the drug on the individual i.e. the response time of a drug can be known in the due course. The commonly used antidepressants are

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)
- Tetracyclic antidepressants
- Serotonin receptor modulators (SRMs)
- Lithium Salts

Venlafaxine is a selective serotonin-norepinephrine reuptake inhibitor with no activity at muscarinic, histaminergic, or adrenergic receptors. Venlafaxine is well tolerated during short- and long-term treatment. The most common adverse effects are nausea, somnolence, and dry

mouth. The overall tolerability of Venlafaxine appears to exceed that of tricyclic antidepressants and compares favorably with that of selective serotonin reuptake inhibitors. Venlafaxine is a novel antidepressant that is appropriate for first-line therapy in patients with major depression.

The proposed work is designed as the bilayer tablet of Venlafaxine HCl. One layer of the bilayer tablet contains the Venlafaxine Hcl as instant release, and the remaining second layer contains the Venlafaxine Hcl as a control release layer for Chronopharmacokinetic aspects of drug delivery to avoid fluctuations of drug concentration. Biological rhythms are thought to be related to the pathogenesis and therapy of various diseases including depression. Here we investigated the influence of circadian rhythms on the antidepressant activity of the dual-action serotonin- noradrenaline reuptake inhibitor (SNRI). Depression is strongly associated with the circadian system. Patients with depression often show a disturbance of the circadian rhythm of various physiological functions (e.g., a sleep disturbance). Depression and circadian disturbance may be physiologically linked and deteriorate synergistically. However, the circadian system has been linked not only to the pathogenesis of depression but also to its therapeutics. The circadian phase was advanced and desynchronized with the sleep-wake cycle in patients with depression, and that phase advance of the sleep-wake cycle exerted an antidepressant effect. Phase entrainment by a bright light in the morning is also effective to improve depressive symptoms. Chronotherapy of depression by the combination of sleep deprivation, sleep phase advance, and bright light treatment induces rapid amelioration in patients with depression. Some antidepressants can interact with and modify the biological clock. In addition, some antidepressants show dosing time-dependent action in animal models and clinical settings. Hence a bilayer tablet of Venlafaxine HCl can release the drug as per the circadian system and could lead to the effective treatment for depression.

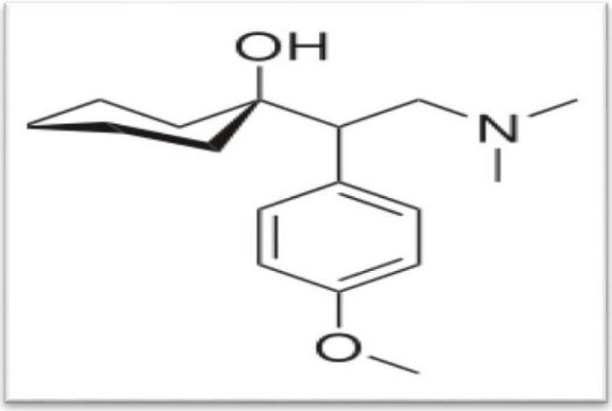

Fig. 1: Structure of venlafaxine HCl.

2. MATERIALS AND METHODOLOGY

2.1 Materials: Venlafaxine HCl was obtained from M/s Alembic Pharma, Vadodara (India) as a gift sample. Important excipients Sodium Starch Glycolate, Cross-Carmilose, Cross-Povidone, Sodium Carboxymethyl cellulose were received from M/s Mapromax Life Sciences Pvt. Ltd., Dehradun. Other excipients, chemicals, and reagents were procured from the Central store of Sagar Institute of Research and Technology-Pharmacy Bhopal.

2.2 METHODOLOGY

2.2.1 Pre-formulation

a) **Physical appearance:** The drug Venlafaxine HCl was examined for its organoleptic properties like state, color, and odor.

b) **Solubility:** For examining the solubility of Venlafaxine HCl, various solvents were used such as water, Phosphate buffer pH 6.8, phosphate buffer pH 7.6, and 0.1N HCl.

c) **Melting Point:** For determination of the melting point, a small amount of powder was placed into a fusion tube. The tube is then placed in the melting point determining apparatus containing castor oil. The temperature of castor oil was gradually increased automatically and the temperature at which powder melt was recorded.

d) **Partition coefficient:** For the determination of the partition coefficient of Venlafaxine HCl, an n-octanol:water system was used. An accurately weighed amount of drug (10mg) was placed in a glass stoppered test tube containing 10ml of n-octanol and 10ml of water. The mixture was shaken on a wrist action shaker for 24hr. Both the phases were separated using a separating funnel and the drug concentration in the aqueous and octanol phase was determined by spectrophotometrically at 224 nm.

e) **UV estimation curve of venlafaxine HCl:** The absorption maxima of Venlafaxine Hydrochloride was determined by running the spectrum of drug solution in a double-beam ultraviolet spectrophotometer. 100mg equivalent weight of Venlafaxine drug sample was dissolved in 100 ml of Distilled water in a volumetric flask. 5 ml of this solution was taken and diluted to 50 ml. The resulting solution was serially diluted to obtain drug concentrations of 5-25 micro g/ml. The absorbances of the solutions were measured against Distilled water as blank at 224nm using the UV spectrophotometer. The plot of absorbance vs. concentration was plotted and the Beer's range was determined.

f) **FT-IR spectroscopy:** This experiment was performed to give sufficient information about the structure of the compound. In our research, identification of Venlafaxine HCl using FT-IR was performed concerning the marker compound. Venlafaxine HCl was

obtained as a white or almost white crystalline powder. It was identified from the result of the IR spectrum as per specification.

g) **Determination of pH:** 1gm of the Powder was dissolved in 100ml of distilled water with sonication and filtered. the pH of the filtrate was checked with a standard glass electrode. The pH determination of Venlafaxine Hydrochloride was done using a digital pH meter.

2.2.2 Flow properties of venlafaxine HCl powder

a. **Bulk and Tapped density:** For bulk density, a known quantity of powder was poured into the measuring cylinder and was carefully leveled powder without compacting. The unsettled apparent volume, Vo, to the nearest graduated unit was recorded. Bulk density was calculated using the formula:

$$Bulk\ density = \frac{bulk\ mass}{bulk\ volume}$$

For tapped density, the glass cylinder containing Venlafaxine HCl was tapped 50 times and density was calculated using the formula:

$$Tappeddensity = \frac{mass}{final\ tapped\ volume}$$

b. **Carr's index, Haussner's ratio, and Angle of repose:** All these parameters were recorded to determine the flow property of the Venlafaxine HCl powder. For Carr's index, the following formula was used.

$$Carr's\ index = \frac{(Tapped\ density - Bulk\ density)}{Bulk\ density} \times 100$$

For Hausner's ratio, the ratio between tapped density and bulk density was calculated. The angle of repose (θ) was calculated by weighing 10 gm of Venlafaxine Hydrochloride powder accurately, and passing through the funnel from the height of 10 cm from the surface and measure the height and diameter by scale. The angle of repose was then calculated using the formula

$$Angle\ of\ repose(\theta) = \tan\theta = \frac{h}{r}$$

2.2 Formulation development: This process was performed in three phases:

i. **Phase-1: Preparation of instant layer of venlafaxine HCl:** Instant release tablets of Venlafaxine Hydrochloride were prepared using the direct compression method, incorporating different super disintegrants such as croscarmellose sodium (Ac-Di-Sol),

crospovidone, and sodium starch glycolate in different concentrations. Avicel PH 102 was used as directly compressible diluents. The above ingredients were weighed and mixed in geometric progression in a dry and clean mortar and the ingredients were passed through mesh #60. Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek' mini-press 16 station rotary compression machine. Nine formulations of Venlafaxine HCl granules were prepared with each formulation containing one of the three disintegrants in different concentrations. Each tablet weighing 75 mg, were obtained.

ii. **Phase-2: Preparation of venlafaxine HCl matrix tablets:** The drug, polymer, and other excipients selected were passed through 40- mesh sieve. Required quantity of drug, polymer, and excipients was weighed and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5min. Polymers used here were HPMC K15 and HPMC K4. For the excipients, Talc and Magnesium stearate.

iii. **Phase-3: Preparation of bilayer tablet of venlafaxine HCl:** An optimized batch of Venlafaxine HCl layers was selected for the preparation of the bilayer tablet. The quantity of powder blend for the sustained release layer was compressed lightly at 10 station Rimek tablet press using 8 mm round concave-faced punch at 10 station tablet press. Over this compressed layer, the required quantity of powder blend for fast release layer was placed and compressed with the hardness in the range of 5-7 kgcm2 to form a bilayer matrix tablet.

2.3 Evaluation parameters: Evaluation was carried out during each phase in our present research.

2.3.1 Evaluation parameters for instant release layer of venlafaxine HCl

- **Shape, Color and Thickness of the tablets:** For the observation of shape, uncoated tablets were examined under a lens, while for the color, tablets were 1observed under the light. For the measurement of thickness, three tablets were randomly selected from each formulation, and individually thickness was measured using Vernier calipers.
- **Flow properties of Pre-compressed powder:** The determination of flow properties was carried out by evaluating parameters like bulk and tapped density, Carr's index, Haussner's ratio, and angle of repose.
- **Weight variation:** For weight variation, twenty tablets were randomly picked from each

formulation and the average weight was calculated. The tablets were weighed individually and compared with the average weight.

- **Hardness and Friability test:** The hardness of the tablets was measured using a Pfizer hardness tester. Results were expressed in Kg/cm^2. For the determination of friability, 20 tablets were selected from each formulation and the friability was calculated using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted, and reweighted, and % friability was calculated.
- **Uniformity of drug content:** For this parameter, ten randomly picked tablets from each formulation (F1 to F9) were finely powdered and powder equivalent to 10 mg of Venlafaxine Hydrochloride was accurately weighed and transferred to 100 ml volumetric flasks containing 100 ml of 0.1N HCL. The flasks were shaken to mix the contents thoroughly. The volume was made up to the mark with 0.1 N HCL and filtered. One ml of the filtrate was suitably diluted and Venlafaxine Hydrochloride content was estimated at 224.0 nm using a double beam UV-visible spectrophotometer.

2.3.2 Evaluation parameters for matrix tablet of Venlafaxine HCl

- **General Appearance and Thickness:** For general appearance, five tablets from different batches were randomly picked and their organoleptic properties were evaluated like color, shape, and odor. For thickness and diameter, five tablets from each batch were selected and individually measure using Vernier Calipers and the average was calculated.
- **Hardness and Friability:** For the determination of hardness, the Monsanto hardness tester (Cadmach) was used. For the parameter of friability, a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.
- **Flow properties of Pre-compressed powder:** The determination of flow properties was carried out by evaluating parameters like bulk and tapped density, Carr's index, Haussner's ratio, and angle of repose.
- **Drug content:** Twenty tablets were selected and the amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to a 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 224.0 nm

using 0.1 N HCl as blank.

- **Dissolution rate studies:** Here, in vitro drug release of the sample was performed using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Venlafaxine HCl Control layer tablet was placed in each basket of dissolution apparatus. The apparatus run for 12 hours. Sample measuring 10ml was withdrawn after 30 min., 1.0 hr, 1.30 hr, 2.0 hr, 4.0 hr, 6.0 hr, 8.0, 10.0 hr, 12 hours using a 10 ml pipette. The fresh dissolution medium was replaced every time with the same quantity of the sample.

2.3.3 Evaluation parameters for bilayer tablet of venlafaxine HCl

- **Shape, Color and Hardness:** For evaluating shape, uncoated tablets were observed under a lens, and for color, tablets were observed under the light. Hardness was measured by randomly selected from each formulation was measured individually using Vernier calipers.
- **Weight variation:** For the determination of weight variation, twenty tablets were randomly picked from each formulation and the average weight was determined. The tablets were weighed individually and compared with the average weight.
- **Hardness and Friability:** Measurement of hardness was performed using the Pfizer hardness tester. For friability, 20 tablets were randomly selected from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted, and reweighted, and % friability was calculated.
- **In-vitro drug release profile:** Bilayer tablets were dispensed to in vitro drug release studies in simulated gastric and intestinal fluids to compute their ability in providing the desired controlled drug delivery. Drug release studies were performed using USP dissolution test apparatus I at 100 rpm,37±0.5°C, and pH 1.2 buffer (900 ml) (i.e. 0.1 N HCl) for 2 hours since the average gastric emptying time is about 2 hours. The dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and the experiment continued for another 10 hours. At different time intervals, 5ml of the samples were withdrawn and replaced with 5ml of drug-free dissolution medium. The samples withdrawn were analyzed by UV spectrophotometer using the multi-component mode of analysis.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation

a) Physical appearance: The drug Venlafaxine HCl powder was evaluated for its organoleptic properties like color and odor and found as an odorless and white powder.

b) Solubility: Solubility was evaluated using a variety of solvents such as water, Phosphate buffer pH 6.8, Phosphate buffer pH 7.6, and 0.1N HCL solution. Through results, it was found out that the solubility of Venlafaxine HCl is good in a 0.1 N HCL solution.

c) Melting Point: The experimental melting point of Venlafaxine HCl was found to be 216°C-220°C. The literature value of melting point was 215-217°C.

d) Partition coefficient: The value of partition coefficient value was determined using the n-octanol:water system and was found to be 0.426

e) UV estimation curve of venlafaxine HCl: This was determined by running the spectrum of drug solution in a double beam spectrophotometer.

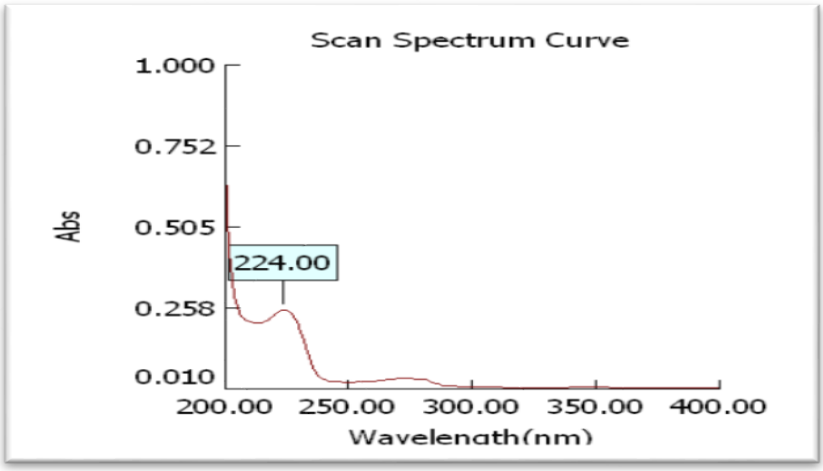

Fig. 2: λmax of venlafaxine HCl.

Table 1: Calibration observation table of Venlafaxine HCl.

S. No.	Conc. µg/ml	Absorbance			
		I	II	III	Average
1	5	0.110	0.114	0.112	0.112
2	10	0.248	0.247	0.249	0.248
3	15	0.337	0.340	0.331	0.337
4	20	0.426	0.425	0.431	0.426
5	25	0.574	0.578	0.575	0.576

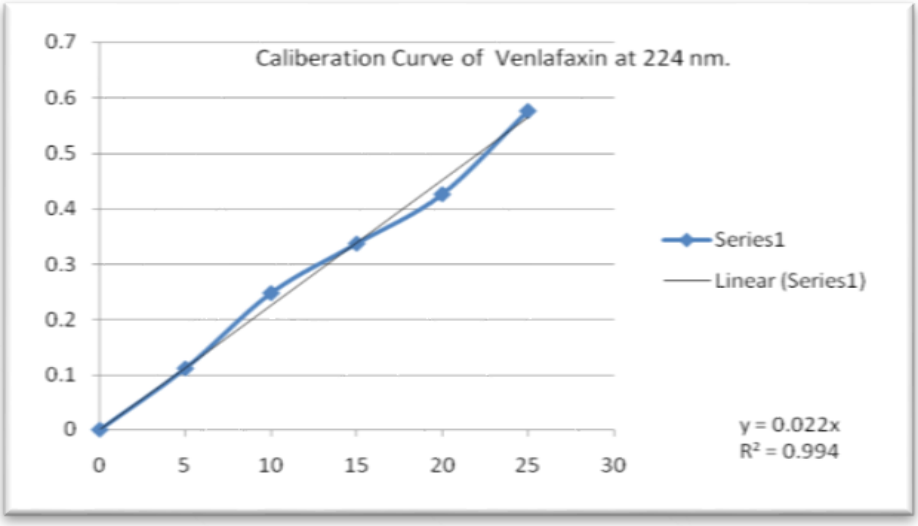

Fig 3: Calibration curve.

f) FT-IR spectroscopy: This was performed to give sufficient information about the structure of the compound

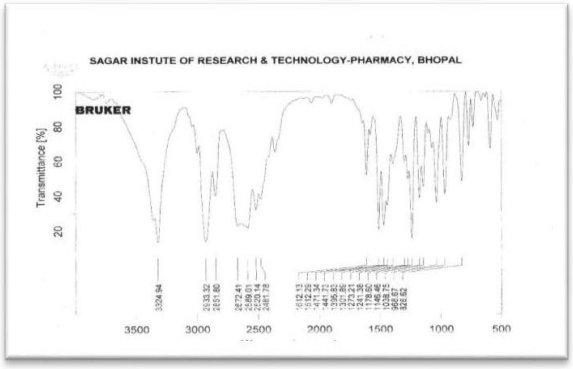

Fig. 4: FT-IR of Venlafaxine HCl.

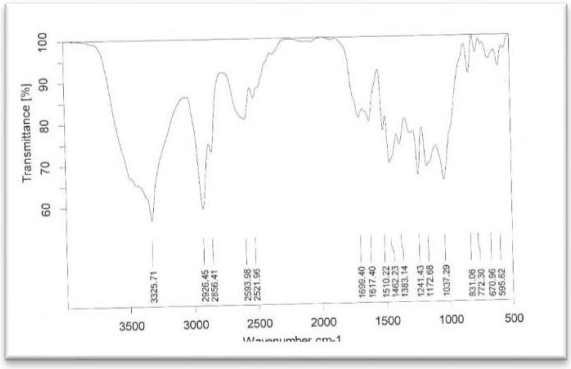

Fig. 5: FT-IR of HPMC-K15.

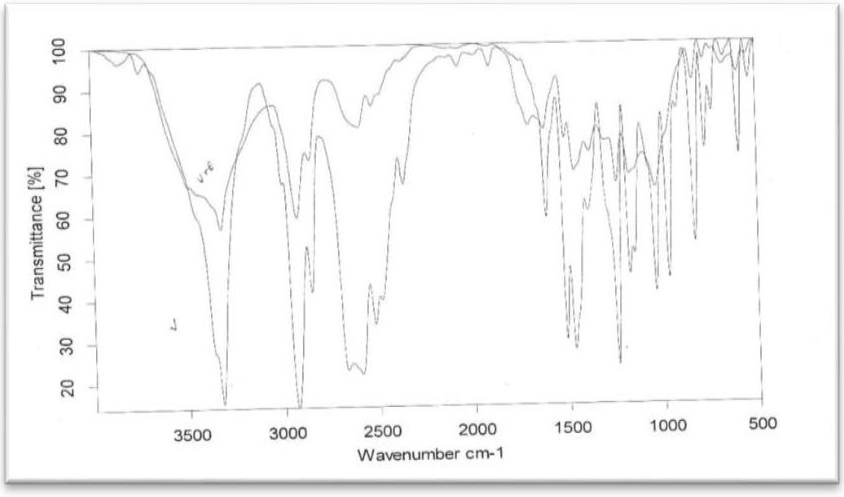

Fig. 6: Overlain FT-IR of Venlafaxine HCl and HPMC-K15.

g) pH determination: The pH determination of Venlafaxine HCl was done by a Digital pH meter and found to be **6.7.**

3.2 Flow properties of venlafaxine HCl

a. Bulk and tapped density: Through experimental study, the bulk and tapped density (50 taps) was found to be 0.243 g/cc and 0.344 g/cc respectively.

b. Carr's index: The value of Carr's index was found to be 29.36% which indicates the poor flow of Venlafaxine HCl.

c. Hausner's value: It was found to be 1.25 indicating cohesiveness of the powder.

d. Angle of Repose (θ): The value of the angle of repose was found to have 30º.

3.3 Formulation development

Table 2 & 3: Various formulations of Instant release and matrix tablet respectively of venlafaxine HCl

Ingredients(mg)	Formulation code								
	TM1	TM2	TM3	TM4	TM5	TM6	TM7	TM8	TM9
Venlafaxine Hydrochloride	25	25	25	25	25	25	25	25	25
Avicel PH102	25	17	11	25	17	11	25	17	11
Crospovidone	20	28	34						
Crosscarmellose sodium [Ac Di Sol]				20	28	34			
Sodium starch glycolate							20	28	34
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	75	75	75	75	75	75	75	75	75

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine Hydrochloride	50	50	50	50	50	50	50	50	
HPMC K 4	80	90	100	-	-	-			
HPMC K 15	-	-	-	80	90				
Lactose	43	33	23						
Talc	3.5	3.5							
Magnesium stearate	3.5								
Total W									

3.4 Evaluation parameters

3.4.1 Evaluation of instant release layer of venlafaxine HCl

- **Shape and Color:** The tablet was observed under a lens and showed a flat**,** circular shape and white color.
- **Pre- compressional parameters:** Here, parameters for flow properties were evaluated.

Table 4: Pre-compressional parameters for venlafaxine HCl instant layer.

Formulation code	Parameters				
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose
TM1	0.315	0.600	47.50	0.525	$28^{O}72'$
TM2	0.318	0.612	48.04	0.520	$26^{O}51'$
TM3	0.322	0.625	48.48	0.515	$28^{O}54'$
TM4	0.315	0.602	47.67	0.523	$25^{O}52'$
TM5	0.326	0.623	47.67	0.523	$28^{O}31'$
TM6	0.356	0.625	43.04	0.570	$27^{O}85'$
TM7	0.345	0.624	44.71	0.553	$27^{O}77'$
TM8	0.315	0.615	48.78	0.512	$28^{O}61'$
TM9	0.347	0.614	43.49	0.565	$26^{O}12'$

- **Post-compressional parameters:** Various parameters, including hardness, friability, drug content were evaluated.

Table 5: Post compressional parameters of Venlafaxine HCl instant release layer.

Formulation code	Hardness test (kg/cm^2) ±SD, n=3	Friability (%) ± SD, n=10	Weight variation (%) n=10	Thickness (mm) ±SD, n=5	Drug content (%) ±SD, n=3
F1	3.13 ± 0.21	0.8217± 0.01	Passes	2.56 ±0.03	99.53±0.42
F2	3.70 ± 0.30	0.7262 ±0.05	Passes	2.59 ±0.05	99.41±0.51
F3	3.51 ± 0.50	0.5314 ±0.03	Passes	2.55 ±0.03	98.77±0.71
F4	3.73 ± 0.29	0.6425 ±0.11	Passes	2.56 ±0.06	99.12±0.49
F5	3.81 ± 0.51	0.6346 ±0.05	Passes	2.55 ±0.03	99.33±0.66
F6	3.50 ± 0.40	0.7114 ±0.16	Passes	2.52 ±0.05	98.51±0.75
F7	3.66 ± 0.29	0.5612 ±0.07	Passes	2.56 ±0.04	99.65±0.42
F8	2.77 ± 0.71	0.8554 ±0.11	Passes	2.54 ±0.05	98.80±0.62
F9	3.12± 0.42	0.7377 ±0.15	Passes	2.56 ±0.04	99.27±0.48

3.4.2 Evaluation of venlafaxine HCl matrix tablet

- **Shape and Color:** The matrix tablet was observed under a lens and showed a flat**,** circular shape and white color.
- **Pre-compressed parameters: Here,** flow properties were observed for the matrix tablet of Venlafaxine HCl.

Table 6: Pre-compressional parameters of Venlafaxine HCl matrix tablet.

- **Post-compressional parameters of Venlafaxine HCl matrix tablet:** Various parameters were evaluated for the matrix tablet of Venlafaxine HCl, such as weight variation, friability, drug content, etc.

Table 7: Post compressional parameters for venlafaxine HCl matrix tablet.

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.89 ±0.03	6.13 ± 0.21	Passes	0.5216± 0.04	98.53±0.48
F2	3.90 ±0.05	6.70 ± 0.30	Passes	0.6325 ±0.04	99.23±0.57
F3	3.89 ±0.03	6.51 ± 0.50	Passes	0.5215 ±0.08	99.77±0.67
F4	3.91 ±0.06	6.73 ± 0.29	Passes	0.6532 ±0.10	99.27±0.23
F5	3.89 ±0.03	6.81 ± 0.51	Passes	0.6485 ±0.04	98.42±0.61
F6	3.90 ±0.05	6.78 ± 0.51	Passes	0.5489 ±0.08	99.57±0.34
F7	3.87 ±0.04	6.80 ± 0.47	Passes	0.5325 ±0.10	99.87±0.56
F8	3.86± 0.04	6.83 ± 0.49	Passes	0.5369 ±0.15	97.37±0.60
F9	3.89± 0.04	6.81 ± 0.50	Passes	0.5425 ±0.15	98.50±0.61

- **In-vitro drug release of matrix tablet:** This evaluation parameter was performed using USP type-II apparatus (paddle type).

Table 8: In-vitro drug release of Venlafaxine HCl matrix tablet.

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08	
1	12.32	10.23	11.45	10.45	10.45	11		
1.5	26.23	22.42	24.23	23.76	31.2			
2	42.45	40.32	45.23	44.23				
3	76.34	66.11	67.21					
4	82.23	77.33	-					
6	82.55	97						
8	83.00							
12								

3.4.3 Evaluation of venlafaxine HCl bi-layer tablet

- **Shape and Color:** Formulations were evaluated for their shape and color. In our results, the shape was found to be a flat, circular shape when observed under a lens. The color was observed under light and was found as a white-colored product.
- **Post-compressional parameters:** Like before, the bilayer tablet of Venlafaxine HCl was also evaluated on many post compressional parameters, such as weight variation, drug content, thickness, etc.

Table 9: Post compressional parameters for venlafaxine HCl bilayer tablet.

Formulation code	Hardness test (kg/cm^2) ±SD, n=3	Friability (%) ± SD, n=10	Weight variation (%) n=10	Thickness (mm) ±SD, n=5	Drug Content (%) ±SD, n=3
TM1	6.13 ± 0.21	0.8217± 0.01	Passes	4.56 ±0.03	99.53±0.42
TM2	6.70 ± 0.30	0.7262 ±0.05	Passes	4.59 ±0.05	99.41±0.51
TM3	6.51 ± 0.50	0.5314 ±0.03	Passes	4.55 ±0.03	98.77±0.71
TM4	6.73 ± 0.29	0.6425 ±0.11	Passes	4.56 ±0.06	99.12±0.49
TM5	6.81 ± 0.51	0.6346 ±0.05	Passes	4.55 ±0.03	99.33±0.66
TM6	6.50 ± 0.40	0.7114 ±0.16	Passes	4.52 ±0.05	98.51±0.75
TM7	6.66 ± 0.29	0.5612 ±0.07	Passes	4.56 ±0.04	99.65±0.42
TM8	6.77 ± 0.71	0.8554 ±0.11	Passes	4.54 ±0.05	98.80±0.62
TM9	6.12± 0.42	0.7377 ±0.15	Passes	4.56 ±0.04	99.27±0.48

- **In-vitro drug release profile:** For our bilayer tablet, in-vitro drug release was performed using USP-apparatus I at 37±0.5°C. Values obtained was tabulated for the optimized formulation F6.

Table 10: In-vitro drug release study of bi-layer tablet of optimized formulation (F6).

Time (min)	√T	log T	Abs.	Conc in ug(abs/slop*d.f)	Amt. in mg	Drug in 900 ml	%CR	Drug in 1 ml	%CDR	Log %CDR
15	3.872	1.176	0.065	59.09	0.059	53.18	20.86	0.209	20.85	1.319
30	5.477	1.477	0.098	89.09	0.089	80.18	31.44	0.314	31.65	1.500
60	7.745	1.778	0.122	110.90	0.111	99.81	39.14	0.391	39.66	1.598
120	10.954	2.079	0.135	122.72	0.123	110.45	43.31	0.433	44.23	1.645
180	13.416	2.255	0.155	140.90	0.141	126.81	49.73	0.497	51.08	1.708
240	15.491	2.380	0.205	186.36	0.186	167.72	65.77	0.658	67.62	1.830
360	18.973	2.556	0.236	214.54	0.215	193.09	75.72	0.757	78.22	1.893
480	21.908	2.681	0.298	270.90	0.271	243.81	95.61	0.956	98.37	1.992
600	24.494	2.778	0.301	273.63	0.274	246.27	96.57	0.966	100.79	2.003
720	26.832	2.857	0.306	278.18	0.278	250.36	98.18	0.982	103.36	2.014

3.4.4 Release kinetics: The release kinetics data for *in-vitro* release profiles were obtained for both matrix tablet and optimized bi-layer tablet of Venlafaxine HCl. These observations were fitted into two model models of data treatment:

- Cumulative percent drug release versus time (zero-order kinetic model)
- Log cumulative percent drug remaining vs time (first-order kinetic model)

3.4.4.1 Release kinetics of matrix tablet of venlafaxine HCl

- **Zero-order kinetic model**

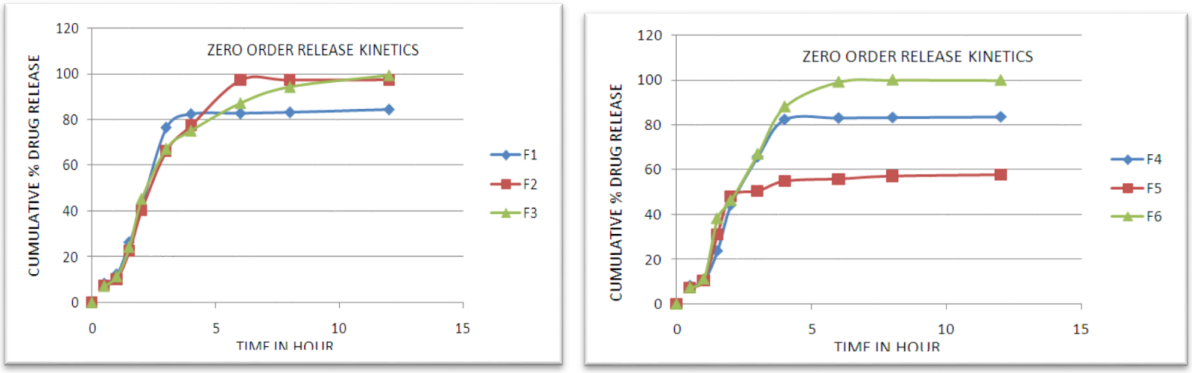

Fig. 7 & 8: Zero-order kinetic drug release of the Venlafaxine HCl matrix tablet (HPMC K-4 and HPMC K-15 respectively as the binders).

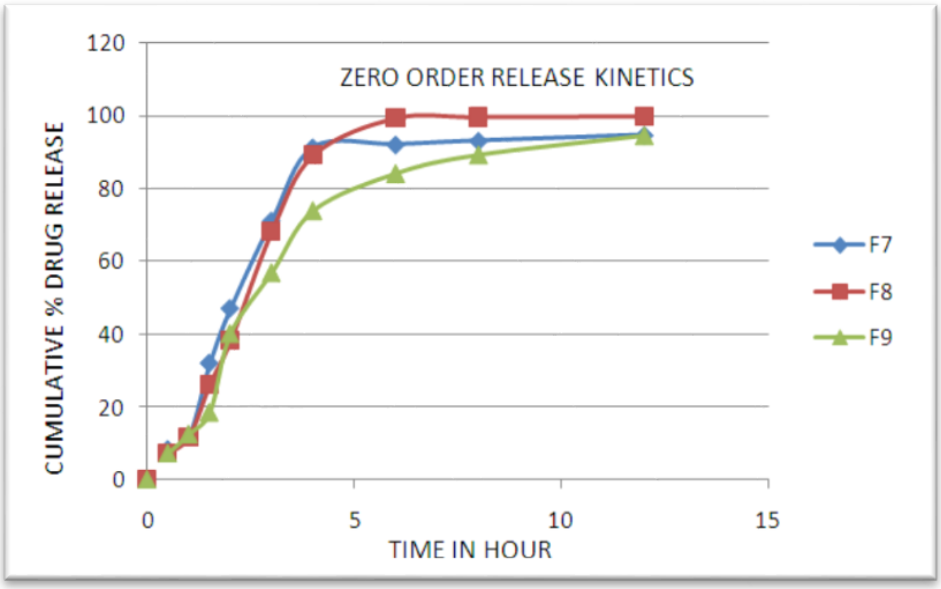

Fig. 9: Zero-order kinetic drug release of the Venlafaxine HCl matrix tablet (HPMC K-4+HPMC K-15).

- **First-order kinetic model**

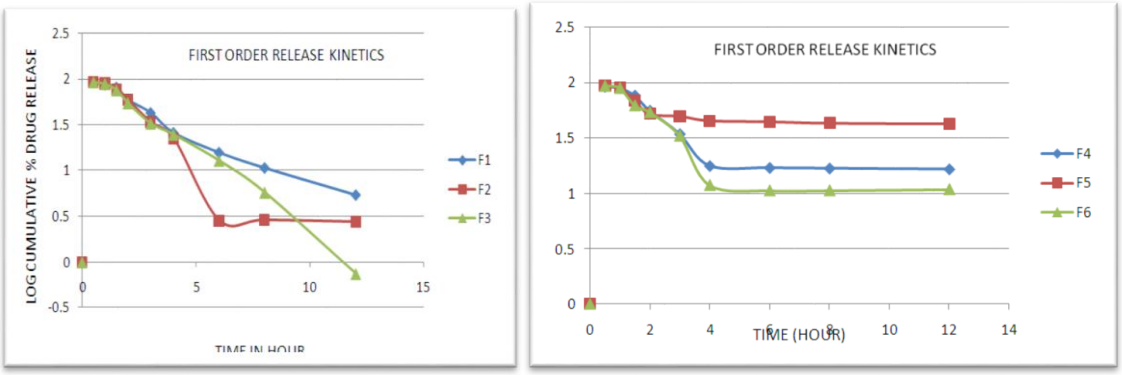

Fig. 10 & 11: First-order kinetic release of Matrix tablet of Venlafaxine HCl (HPMC K-4 & HPMC K-15 as the binders respectively).

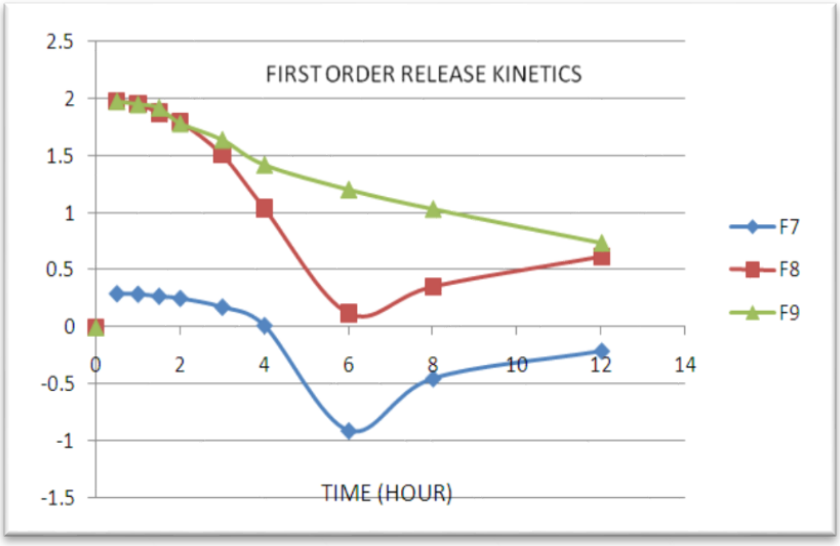

Fig. 12: First order kinetic release of matrix tablet of Venlafaxine HCl (HPMC K-4 + HPMC K-15 as the binders).

3.4.4.2 Release kinetics of optimized formulation F6 bilayer tablet of Venlafaxine HCl

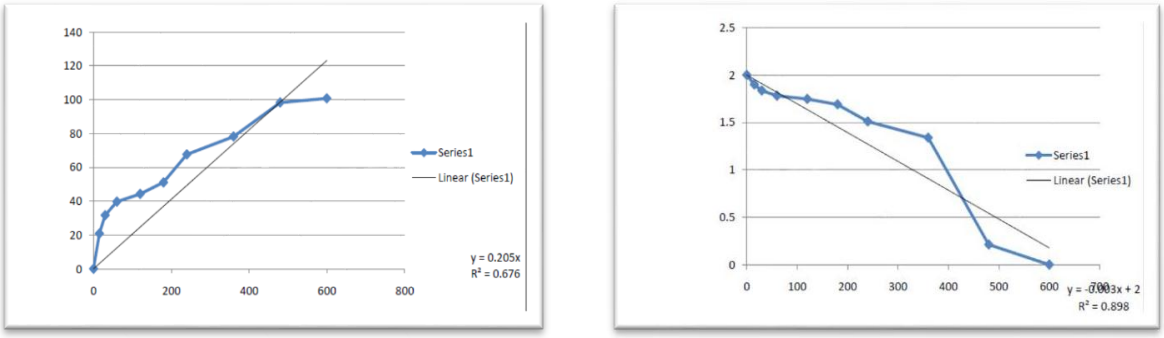

Fig. 13 & 14: Zero-order and First-order release respectively of F6 bi-layer tablet.

4 CONCLUSION

Through this present study, we can satisfactorily conclude that Venlafaxine HCl in the form of a bi-layer tablet to avoid drug fluctuation and for chronotherapy shows a tremendous amount of improvement. Through our experiments, we can conclude that bi- layer tablet of Venlafaxine HCl shows better results in chronotherapy than plain Venlafaxine HCl. Usage of polymers like HPMC K-4 and HPMC K-15 improved the *in- vivo* drug release and overall better results than a conventional tablet of Venlafaxine HCl.

In vitro data was obtained for Bilayer tablet of Venlafaxine Hydrochloride displayed initial burst release due to instant release of drug followed by prolonged drug release. Tablets of different release kinetics could be obtained by varying the formulation variables. These observations lead us to the conclusion that Venlafaxine HCl is the most suitable drug candidate for anti-depressants and the bi-layer tablet technique seems to be a promising drug delivery system for those drugs whose pharmacokinetic parameters can be affected by circadian rhythm.

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