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Formulation and In Vitro Evaluation of Sustained Release Tablets of Venlafaxine Hydrochloride by Porous Osmotic Technology

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Abstract- The present study involves the development of porous osmotic tablets of Venlafaxine Hydrochloride in order to release the drug in sustained and predictable manner. Venlafaxine Hydrochloride is a unique antidepressant that differs structurally from other currently available antidepressants. Short biological half life, low bioavailability and frequent administration of drug led for rational development of 300mg sustained release osmotic tablets of Venlafaxine Hydrochloride that releases the drug and maintain the plasma drug concentration for more than 8hrs. The method of preparation of these SR osmotic tablets follows osmotic bursting pump model. Polymers like hydroxy propyl methyl cellulose (HPMC) K15M with lactose as diluents, magnesium stearate as glidant and talc as lubricant were selected for sustaining the drug release. The drug to polymer ratio was 1:1. The tablets were prepared by wet granulation method. A film coating with a semi permeable membrane of 2% m/v cellulose acetate in acetone was done to the core tablets. Hence, the developed formulation provides advantages of less steps of manufacturing procedure, no need of laser drilling, and economical all of these made the procedure easily amenable to mass production using conventional tablet machines. All polymers and excipients used in optimized formula were found to be compatible with the drug and it was confirmed by FT-IR studies. Drug release from the developed formulations was independent of pH and dependent only on osmotic pressure. Kinetic modeling of in vitro drug release data follows first order release plot.

Index Terms- Osmotic bursting pump, Sustained release formulation, Venlafaxine Hydrochloride, Organic osmagent, Wet granulation.

I. INTRODUCTION[1]

Osmotic pressure is a most important colligative property where the concentration of solution is independent of solute property. Osmotic pressure of a solution is the external pressure that must be applied to the solution in order to prevent it being diluted by the entry of solvent via a process known as Osmosis. In other words, Osmosis refers to the process of movement of solvent from lower concentration of solute towards higher concentration of solute across a semi permeable membrane. Such membrane is only permeable to solvent molecule. Because only solvent can pass through the semi permeable membrane, the driving force for the osmosis arises from the inequity of the chemical potentials of the solvent on opposing side of the membrane.

Advantages [2]

Osmotic pumps offer many advantages over other controlled drug delivery system:

- Osmotic system is independent of pH and other physiological parameters to a large extent.
- Reduce rate of rise of drug concentration in blood.
- Sustained & consistent blood levels within the therapeutic window.

Disadvantages [3]

- Less flexibility in accurate dose adjustment.
- Poor In vitro In vivo correlation (IVIVC)
- Increased potential for first pass clearance.

Principle of Osmosis [2, 4, 5]

Abbe Nollet first reported osmotic effect in 1748, but Pfeffer (1877) had been pioneer of quantitative measurement of osmotic effect. He measured the effect in 1877 by utilizing a membrane, which is selectively permeable to water but impermeable to sugar. The membrane separated sugar solution from pure water.

Pfeffer observed a flow of water into the sugar solution that was halted when a pressure P was applied to the sugar solution. Pfeffer postulated that this pressure, the osmotic pressure (π) of the sugar solution is directly proportional to the solution concentration and absolute temperature.

Van't Hoff established the analogy between the pfeffer results and the ideal gas laws by the expression:

$$\pi = n_2 RT \text{ ----------(1)}$$

Where n_2 represents the molar concentration of sugar (or other solute) in the solution, R depicts the gas constant, and T the absolute temperature.

The Van't Hoff equation presents a god means for calculating the osmotic pressure of solutes across perfect semi permeable membranes and is accurate for low solute concentrations. But in case if the membrane is not completely semi permeable and permits passage for solute along with solvent, the osmotic pressure calculated by equation will be more when compared with experiment value. Concentrated solutions also show deviations from these ideal equations.

A number of researchers (Reid, 1966; Hughes, 1961) have discussed, modified and brought about more accurate expression of this equation. Another method of obtaining a good approximation of osmotic pressure is by utilizing vapour pressure

measurements and by using the expression:

$$\pi = RT\ln(P_0/P)/v \text{ ————(2)}$$

Where,

P_0 = vapour pressure of the pure solvent

P = vapour pressure of the solution

V = molar volume of solvent

As vapour pressures can be measured with less effort than osmotic pressure, this expression is frequently used. Osmotic pressure for soluble solute is extremely high. This high osmotic pressure is responsible for high water flow across semi permeable membrane. The rate of water flow dictated by osmotic pressure can be given by equation:

$$Dv/dt = A\theta\Delta\pi/l \text{ --------(3)}$$

Where,

Dv/dt = water flow across the membrane area A and thickness l with permeabilityθ.

$\Delta\pi$ =Depicts the difference in osmotic pressure between the two solutions on either side of membrane.

This equation is strictly applicable for perfect semi permeable membrane, which is completely impermeable to solutes.

Osmotic Drug Delivery System [6]

- Elementary Osmotic Pump
- Push-Pull Osmotic Pump (PPOP)
- Controlled Porosity Osmotic Pump (CPOP)
- Monolithic Osmotic Systems
- Colon Targeted Oral Osmotic System (OROS-CT)
- Sandwiched Osmotic Tablets (SOTS)
- Bursting Osmotic Pump
- Liquid-Oral Osmotic (L-OROS) System
- Osmotic Matrix (OSMAT)

Formulation aspects [6]

The various formulation factors affecting drug release from oral osmotic pumps are:

- ***Drug solubility:***

Solubility of the drug selected for osmotic formulation is a very important factor as the solubility is directly proportional to the release kinetics from the osmotic system. Drugs with high and low water solubility do not form a good candidate for osmotic delivery. If needed, the solubility of drug in the core can be modulated by incorporating suitable solubility modulators to control the release of drug from the osmotic system**.** Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation:

$$F(z) = 1 - S/\rho \text{ ---------- (4)}$$

Where, F (z) is the fraction released by zero-order kinetics, S is the solubility of drug (g/cm3).

- ***Coating Membrane:***

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. , the importance of rate controlling membrane in the drug release can be recognized. The polymers used for coating of the osmotic system should be semi-permeable in nature. Therefore, any polymer that is permeable to water but impermeable to solute can be used for this purpose. The polymers commonly used for this purpose are cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate and cellulose acetate butyrate.

Cellulose acetate films are insoluble yet semi permeable and allow water to pass through the coating. Water permeability of cellulose acetate films depends on the amount and type of acetylation on the cellulose backbone. As the acetyl content increases, the permeability decreases, solvent resistance increases and the glass transition temperature increases. To ensure that the coating is able to resist the pressure within the osmotic system, thickness of membrane is usually kept between 200 .300 µm**.** is the density (g/cm3) of the core tablet. Drugs with a solubility of ≤0.05 g/cm3 would be released with ≥ 95% zero-order kinetics.

- ***Osmotic Pressure:***

Drugs selected as candidate for formulation as an osmotic system, should possess osmotic pressure. The release rate of drug from osmotic system is directly proportional to the osmotic pressure of the core formulation. If the drug does not possess sufficient osmotic pressure, an osmagent like sodium chloride, glucose, sucrose, glycine, etc. can be added in the core formulation to control the release of drug from the osmotic system.

- ***Delivery Orifice:***

Release of drug from osmotic system is carried out with the help of delivery orifice, thus the size of delivery orifice is a critical factor in controlling the release of drug. The size of the delivery orifice has to be optimized as a small delivery orifice may affect zero order kinetics; but if the delivery orifice is too small, the hydrostatic pressure may not be relieved causing deformation of the system or unpredictable drug release profile, while if delivery orifice is too large, solute diffusion may take place. There are mathematical calculations that can be used to calculate the optimum size of the delivery orifice. Delivery orifice is made in the osmotic system either by mechanical drilling or by laser drilling in the semi permeable membrane of theo-osmotic system. In case of CPOP, the in situ pore formation takes place depending on the concentration of the pore-forming agent in the coating solution

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Antidepressants [7, 8]

Antidepressants are psychiatric medications given to patients with depressive disorders to alleviate symptoms. They

correct chemical imbalances of neurotransmitters in the brain which probably cause changes in mood and behavior. Antidepressants may be used for a wide range of psychiatric conditions, including social anxiety disorder, anxiety disorders, and dysthymia (mild chronic depression).

Serotonin and nor adrenaline Reuptake Inhibitors (SNRIs)

A class of drugs used to treat major depression, mood disorders, and possibly but less commonly ADHD (attention deficit hyperactivity disorder), obsessive compulsive disorder, anxiety disorders, menopausal symptoms, fibromyalgia, and chronic neuropathic pain. SNRIs raise levels of serotonin and nor epinephrine, two neurotransmitters in the brain - they both play a key role in stabilizing mood.

Examples of Serotonin Nor epinephrine Reuptake Inhibitors are: Duloxetine (Cymbalta), Venlafaxine(Effexor) and Desvenlafaxine (Pristiq). Desvenlafaxine was found to be especially helpful in alleviating the symptoms of major depression in menopausal or pre-menopausal women, according to a study carried out by a team at Virginia Commonwealth University.

The first and most commonly used SNRI. It was introduced by Wyeth in 1994. The reuptake effects of Venlafaxine are dose-dependent. Venlafaxine selectively inhibits the neuronal re-uptake of neither serotonin, nor epinephrine and to a lesser extent dopamine. It has minimal affinity for muscarinic, histamine or α_1-adrenergic receptors. It appears to be as effective as standard antidepressants with a lower incidence of the anti cholinergic side effects.

II. MATERIALS AND METHODOLOGY

1. Materials: Venlafaxine hydrochloride, HPMC K_4M, K15M, E15M, Cellulose acetate, Sodium CMC, Mannitol, Lactose, Acetone, PEG-400, PVP K30, Magnesium stearate, Talc.

2. Equipments: Digital balance (Essen, Bangalore), p^H meter, UV Spectrophotometer, Dissolution Apparatus (Lab India), Multi station tablet punching machine (Karnavati, RIMEK mini press), R&D coater (VJ instruments), Mechanical stirrer (REMI), Glassware (Borosil).

Analytical Methods

1. Determination of λmax of Venlafaxine Hydrochloride in 0.1N Hcl and pH 6.8 Phosphate buffer:

Dissolve 8.5ml of Hcl in 1000ml of distilled water. 1mg of venlafaxine Hcl was accurately weighed and was dissolved in the 10ml of 0.1N Hcl solution. The resulting stock solution containing 10mcg/ml was scanned between 200-400nm. The similar procedure was carried out for pH6.8 buffer solution.

2. Construction of calibration curve of Venlafaxine Hydrochloride in buffer solution:

Accurately weigh 100mg of Venlafaxine Hcl and dissolve it in 100 ml of phosphate buffer. This is regarded as the stock 1 solution with 1000mcg/ml. Then take 5ml of the above solution and place it in 50 ml of the buffer which is regarded as stock 2 solution with 100mcg/ml. Lastly take 1ml of the stock 2 solution and mix it with 10 ml of the buffer which is regarded as stock 3 solution with 10mcg/ml. This stock solution was scanned between 200-400nm. Further, more serial dilutions can also be made for accurate results.

Pre-formulation Studies[9]

Pre-formulation testing is the first step in the rationale development of dosage forms of a drug. It can be defined as an investigation of physical and chemical properties of drug substance, alone and when in combined with excipients. The overall objective of the pre-formulation testing is to generate information useful to the formulator in developing stable and bio availability dosage forms which can be mass produced.

i. Bulk Density (D_b)
ii. ii. Tapped Density (D_t)
iii. Angle of Repose (Θ)
iv. Carr's index (or) % Compressibility
v. Hausner ratio

Formulation Development of SR Osmotic Tablets of Venlafaxine Hcl [10]

The formulation development in the present study was done by osmotic bursting pump. The solubility characteristics were considered more important in the development of a formulation.

1. ***Preparation Of Core Tablets***

Accurately weighed quantities of ingredients were passed through sieve No. 85. All the ingredients, except lubricant (Magnesium stearate), glidant (Talc) and binder polyvinylpyrrolidone (PVP), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution of 10% (m/V) PVP, and granulated through sieve No. 18 and dried in a hot air oven at 60^0 c for sufficient time (3 to 4 hours) so that the moisture content of the granules reached 2–4%. The dried granules were passed through sieve No. 26 and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (300 mg each) using 9mm diameter, deep concave punches. The compression force was adjusted to give tablets with approximately 4.5-5kg/cm^2 hardness on a Monsanto tablet hardness tester.

2. ***Coating Of Core Tablets***

Core tablets were film coated with either a semi permeable membrane of 2% (m/V) cellulose acetate (CA) in acetone with castor oil (20%, m/m, total solid CA) as plasticizer using a conventional laboratory model, stainless steel, 10-cm pear shaped, baffled coating pan.

a. Preparation of coating solution:

Required quantity of cellulose acetate was accurately weighed and dissolved in a beaker containing acetone using mechanical stirrer. The stirring was continued till a clear solution was formed. PEG 400 was separately dissolved in a beaker containing measured quantity of water and was added slowly to cellulose acetate mixture with stirring.

b. Coating procedure:

Core tablets of Venlafaxine Hcl were placed along with placebo tablets the coating pan was rotated at 60 rpm and heated air was passed through the tablet bed. Coating process was

started once the outlet temperature reached 28^{o}C. Coating solution was sprayed at the rate of 12-14 ml/min and optimizing the air pressure was kept at 30-35 lb/in^{2}. The outlet temperature was maintained at 28^{o}C by keeping the inlet temperature at 45-50 ^{o}C. Coating was continued until desired weight gain was obtained on active tablets. In all cases active tablets were dried at 60^{o}C for 16 h before further evaluations.

Formulation Chart

The drug Venlafaxine Hcl was formulated in 12 different formulations with different polymers and excipients ratio's (1:1, 1:2 and 1:0.5). The weight of the tablet is 300mg which are tabulated as follows:

The formulations F1-F3 contained drug and K4M polymer and lactose in 1:1, 1:2 and 1:0.5. The formulations F4-F6 contained drug and K15M polymer and lactose with the same ratios mentioned above. F4 is regarded as the optimized formulation.

Ingredients (mg)	Core Tablet		
	F1,F4(1:1)	F2,F5(1:2)	F3,F6(1:0.5)
Venlafaxine Hcl	75	75	75
HPMC K4M, K15M	75	150	37.5
PVP(K30)	Q.S	Q.S	Q.S
Lactose	144	69	181.5
Magnesium Stearate	3	3	3
Talc	3	3	3

Table 1: F1-F6 with different Drug: Polymer Ratio's

The formulations F7-F9 contained drug with sodium CMC and lactose, whereas the formulations F10-F12 contained drug with E15 polymer and mannitol in the same ratios as mentioned earlier.

Ingredients (mg)	Core Tablet		
	F7,F10(1:1	F8,F11(1:2)	F9,F12(1:0.5)
Venlafaxine Hcl	75	75	75
Sodium CMC/E15	75	150	37.5
PVP(K30)	Q.S	Q.S	Q.S
Lactose/Mannitol	144	69	181.5
Magnesium Stearate	3	3	3
Talc	3	3	3

Table 2: Formulations With Different Drug: Polymer Ratio's

Ingredients	Coating Ratio's		
	C1(W/V)	C2(W/V)	C3(W/V)
Cellulose Acetate	2%	2%	2%
PEG 400	5%	5%	5%
Acetone	90:10	90:10	90:10

Table 3: Coating Composition

Post Formulation Parameters:

1. Weight variation:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation.

2. Hardness:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^{2}.

3. Thickness:

Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper in kg/cm$^{2.}$

4. Friability (F):

Friability of the tablet determined using Roche friabilator. The friability (F) is given by the formula

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

5. In-Vitro drug release:

Release of the drug *in vitro*, was determined by estimating the dissolution profile.

Dissolution test: USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, acid buffer 0.1N HCL for 2 hrs, 6.8 pH buffer for 6 hours, (each 900 ml) was used as a dissolution medium.

6. Assay:

10 tablets were weighed and triturated. The tablet triturate equivalent to 8 mg of the drug was weighed accurately, dissolved in phosphate buffer and diluted to 100 ml with the same. Further dilutions were done suitably to get a concentration of 10 µg/ ml with phosphate buffer. Absorbance was read at 224 nm against the reagent blank, and the concentrations of Venlafaxine Hcl in µg/ ml was determined by using the regression equation.

III. RESULTS & DISCUSSION

Analytical methods for drug estimation

Table 4: Calibration Curve of Venlafaxine Hcl in 0.1 N Hcl at 228nm

S.No	Concentration (mcg/ml)	Absorbance
1.	5	0.18
2.	10	0.312
3.	15	0.458
4.	20	0.619
5.	25	0.849
6.	30	1.061

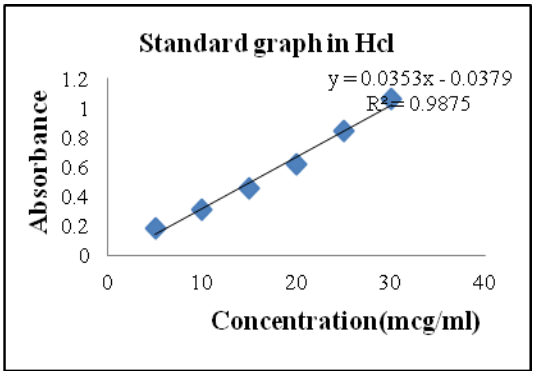

Fig.1. Standard Graph of Venlafaxine Hcl in 0.1N Hcl

Table 5: Calibration Curve of Venlafaxine Hcl in pH 6.8 Phosphate Buffer at 224nm

S.No	Concentration (Mcg/Ml)	Absorbance
1.	5	0.181
2.	10	0.32
3.	20	0.51
4.	30	0.645
5.	40	0.849

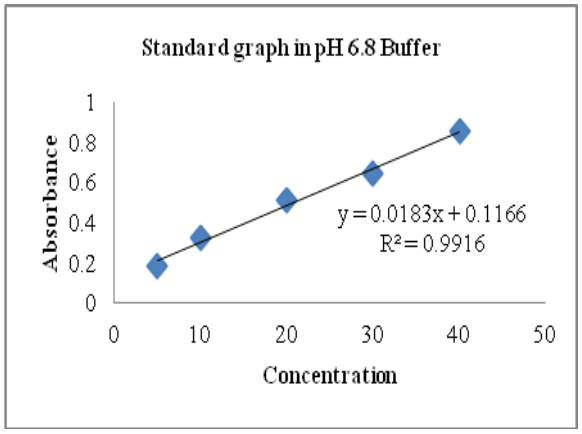

Fig.2.Standard Graph of Venlafaxine Hcl in pH 6.8 Phosphate Buffer

Table 6: Pre- Compression Results

Pre-Compression Parameters					
Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner Ratio	Angle of Repose(Θ)
F_1	0.212	0.234	8.55	1.10	23.45
F_2	0.231	0.245	5.71	1.06	24.54
F_3	0.256	0.301	14.95	1.17	25.50
F_4	0.264	0.312	15.38	1.18	26.33
F_5	0.231	0.292	20.98	1.26	25.45
F_6	0.227	0.275	17.45	1.21	26.34
F_7	0.245	0.286	14.33	1.16	25.06
F_8	0.265	0.306	13.39	1.11	25.35
F_9	0.243	0.298	18.45	1.18	24.38
F10	0.285	0.331	13.89	1.17	25.60
F11	0.273	0.265	16.55	1.12	23.22
F12	0.257	0.242	13.25	1.09	24.58

Table 7: Post Compression Results

Formulation	Weight Variation(Mg)	Hardness (Kg/Cm^2)	Thickness (Mm)	Friability (%)	Assay (%)
F1	298±1.13	4.33±0.21	2.1±0.07	0.34	98.21
F2	301±1.17	4.76±0.20	2.0±0.05	0.49	98.34
F3	299±1.11	4.25±0.23	2.2±0.02	0.34	101.4
F4	300±1.15	4.98±0.22	2.2±0.1	0.47	99.34
F5	299±1.12	4.86±0.21	2.0±0.03	0.34	99.25
F6	302±1.15	4.63±0.21	2.1±0.03	0.49	98.38
F7	298±1.19	4.90±0.23	2.4±0.06	0.47	99.32
F8	300±1.14	4.43±0.22	2.3±0.02	0.36	98.67
F9	302±1.12	4.95±0.24	2.3±0.01	0.44	98.25
F10	299±1.15	4.58±0.23	2.1±0.07	0.39	99.37
F11	298±1.18	4.32±0.21	2.2±0.05	0.43	98.52
F12	298±1.16	4.71±0.22	2.2±0.04	0.38	99.78

In vitro Dissolution Profile of Venlafaxine Hydrochloride Osmotic Formulation F4

Time	F4
0	0
0.5	12.01
1	34.5
2	56.5
3	72.5
4	87.8
6	94.6
8	96.5

Table 8: Dissolution Profile of F4

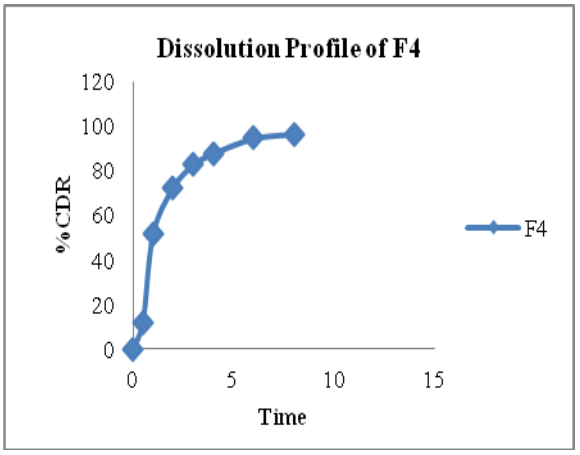

Fig.3.Dissolution Profile of Optimized F4

Drug Compatibility Studies:

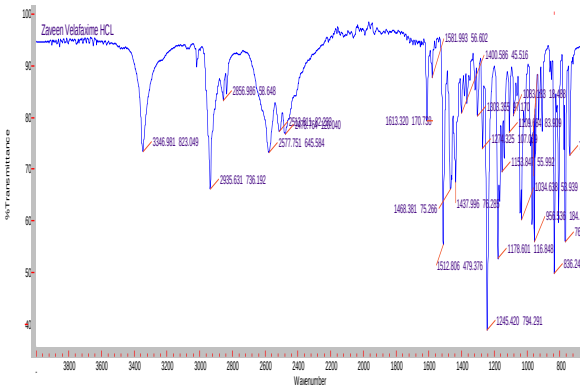

Fig.4. FTIR of Venlafaxine Pure Drug

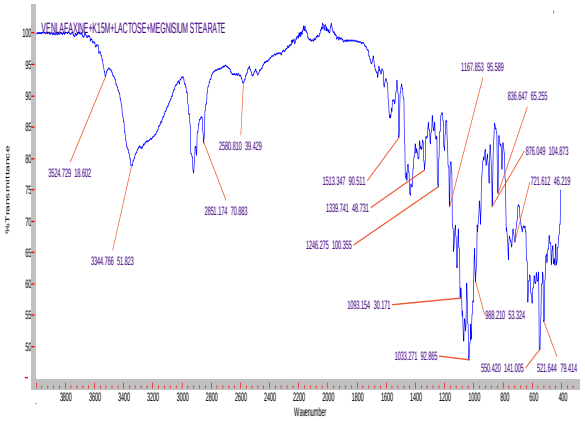

Fig 5: FTIR of Optimized Formulation F4

Drug/ Polymer	O-H Stretch	C-H Aromatic	C-H Aliphatic	C-O Stretch
Venlafaxine Hydrochloride	3346.98	2935.63	2856.98	1083.63
HPMC $K_{15}M$	3345.35	2936.58	2581.88	1034.59
Lactose	3344.86	2936.45	-	1033.93
Magnesium Stearate	3346.31	2917.26	2850.64	1036.80
Optimized Formulation F4	3344.76	2851.17	2580.81	1033.27

Table 9: IR Peaks of Venlafaxine Hcl and Excipients

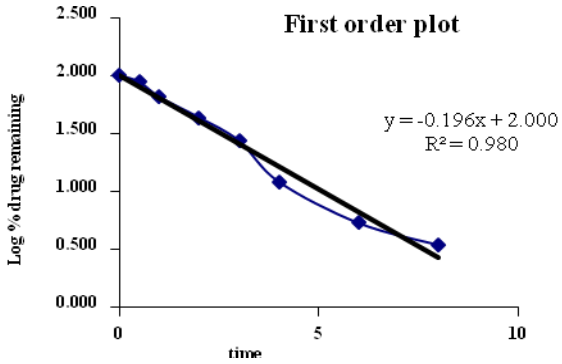

Fig.6. First Order Release of Optimized Formulation F4

Evaluation Parameters for osmotic Tablets of Venlafaxine Hcl

1. ***Pre-compression parameters:***

The values for angle of repose were found in the range of 23°-26°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.21 to 0.28 (gm/cc) and 0.23 to 0.33 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 5.7% to 20.9%. The Hausner ratio fall in the range of 1.06 to 1.26. From the result, it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture (Table 6).

2. ***Post compression Parameters***

- Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 5.4. The average weight of the tablet is approximately in range 298 to 302, so the permissible limit is ±5% (250mg or more). The results of the test showed that, the tablet weights were within the pharmacopoeia limits (Table 7).

- **Hardness test:**

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in the Table 7. The results showed that the hardness of the tablets is in range of 4.00 to 5.00 kg/cm^2, which was within IP limits.

- **Thickness:**

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 7. The result showed that thickness of the tablet is raging from 2 to 2.5.

- **Friability:**

Tablets of each batch were evaluated for percentage friability and the data's were shown. The average friability of all the formulations lies in the range of 0.5 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets (Table 7).

- **In vitro dissolution studies:**

Finally, the tablets were evaluated for *in vitro* dissolution studies in acid buffer (pH-1.2) for 2 hours followed by pH 6.8 buffer for 6 hours. The results were shown in the Table 8.

Formulations F1- F3 contained Venlafaxine hcl and K_4M polymer in different ratio's i. e 1:1, 1:2 and 1:0.5 but could not release maximum amount of drug from formulations till 8 hrs of dissolution study. Formulations F4-F6 contained Venlafaxine Hcl and $K_{15}M$ in different ratio's and a sustained drug release till 8 hours of dissolution study was carried out. Formulation F4 has showed maximum amount of drug released with drug release of 98.7% at 8th hour, so it is chosen as an optimized formulation. Formulations F7-F9 contained Venlafaxine Hcl and Sodium CMC wherein, complete release of the drug was found within 6 hours of dissolution study. The reason may be due to increase in concentration of pore forming agent (10%). Formulations F10-F12 contained the drug, HPMC E15 and Mannitol prepared by direct compression technique. The drug got completely solubilize within 2 hours.

- **Assay:**

The percentage drug content of Venlafaxine Hcl osmotic tablets was found to be between 98-102%, which was within the acceptable limits. This result indicates that there was uniform distribution of the drug throughout the batch.

IV. CONCLUSION

The sustained release tablets of Venlafaxine Hydrochloride were prepared by porous osmotic technology. Osmotic bursting pump technique was implemented to prepare sustained release tablets of Venlafaxine Hydrochloride. 12 Venlafaxine Hcl sustained release tablets were successfully formulated with HPMC K4M, K15M, E15, Sodium CMC and Mannitol in different concentrations of 1:1, 1:2 and 1:0.5. Out of which F4 was the optimized formulation. An optimum concentration of drug and polymer HPMC K15M in 1:1 ratio was able to provide the desired release with innovator profile requirement. Developed formulation is expected to reduce the frequency of administration thereby reduces the chance of adverse effect associated with frequent administration of Venlafaxine Hcl tablets.

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