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DEVELOPMENT AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM FOR VENLAFAXINE HYDROCHLORIDE AS BILAYER TABLET

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ABSTRACT: Present research work aims to develop venlafaxine hydrochloride gastro retentive tablets for prolonged release and increased gastric retention time. Venlafaxine is an antidepressant of the serotonin nor- epinephrine reuptake inhibitor (SNRI) class. Bioavailability is 45% following oral administration and half life is 5 hours. To study the effect of formulation variables on drug release and buoyancy properties of the sustained release venlafaxine hydrochloride gastro retentive floating drug delivery system, the floating matrix tablets of venlafaxine hydrochloride were prepared by bilayer tablet technology with sustained and floating layers. The different hydrophilic polymers for sustained release layer studied, were HPMC K 4M, HPMC K 15M, xanthan gum studied in order to obtain the desired sustained release up to 12 hrs and the effervescent component of floating layer was sodium bicarbonate along with HPMC K 100M. Drug compatibility with excipients was checked by FTIR studies. The formulation optimization batches were studied for physical parameters and floating behavior, dissolution studies and kinetics of drug release. Hardness of tablets was kept 6 kg/cm^2. The effect of concentration and type of polymer on drug release rate were studied. The optimized formulation was also tested for accelerated stability studies at 40 ^{0}C /75% RH for one month and the formulation was checked for drug release study, uniformity of content and floating lag time after 30 days. *In vitro* buoyancy study results found to be 60 to 70 sec floating lag time and 12 hours total floating time respectively.

INTRODUCTION: Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site, thus ensuring its optimal bioavailability[1-2]. Controlled drug delivery system with gastrointestinal retentive feature releases the drug in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract[3].

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Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many factors[4]. Influence of these factors makes the drug absorption unpredictable and inconsistent. Using GRDDS the drug release can be made to happen specifically in the gastric region thus minimizing the influence of the factors leading to more consistent delivery of the drugs.

In general, drug delivery to systemic circulation through oral route is more convenient and preferred because of improved therapeutic advantage, low cost of drug, patient compliance and adjustment in formulation according to need[5]. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the

development of oral sustained/controlled release formulations is an attempt to release the drug slowly into the GIT and maintain an effective drug concentration in the systemic circulation for a long time[6]. Gastric fluids facilitate and improve the disintegration for slow dissolving drugs and the drugs which show local effect within the stomach[7]. Salient features of upper gastrointestinal tract such as stomach length 0.2 m, transit time varying from 1-4 h and absorbing surface area of 0.1 m^2 make it the site for absorption as well[8]. In addition to that the drug absorption can also occur from the entire GIT following the release from the GRDDS system in the gastric region

Site-specific drug delivery using novel formulation designs would improve local therapy in the GI tract, optimize systemic absorption and would minimize premature drug degradation [9]. These efforts resulted in floating drug delivery system (FDDSs) that were designed in large part based on the following approaches: (a) low-density form of the FDDS that causes buoyancy above gastric fluid (b) high-density FDDS that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa; (d) slowed motility of the GIT by concomitant administration of drugs or pharmaceutical excipients with motility suppressant property; and (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.[10].

The limitations associated with conventional gastro-retentive system could be minimized by using floating beads to prolong the gastric transit time by ionotropic gelation of two or more polysaccharides[11]. The use of naturally occurring plant-based pharmaceutical excipients has become very important in the development of controlled release dosage forms, because of their ability to produce a wide range of material based on their properties and molecular weight[12]. (This sentence is not required) Criteria for selection of a drug candidate for GRDF include its ability to have absorption from upper GIT which is possible for drugs having low pKa that remain unionized in stomach thus showing better absorption.

The main application of floating drug delivery system includes sustained and site-specific drug delivery.

Venlafaxine is used primarily for the treatment of depression, general anxiety disorder, social phobia, panic disorder and vasomotor symptoms. Venlafaxine is an antidepressant of the serotonin nor- epinephrine reuptake inhibitor (SNRI) class. It belongs to BCS Class I (highly permeable and highly soluble). It has half life of four hours with pKa of 9.4. It is freely soluble in water and methanol, soluble in anhydrous ethanol, slightly soluble or practically insoluble in acetone. It has bioavailability of 10-45 % with protin binding 27%, and clearance by hepatic and renal route. From the drug profile it can be considered as the drug venlafaxine fulfills the criteria for selection as candidate for floating drug delivery system.

MATERIALS AND METHODS:

Materials:

Venlafaxine HCl was obtained as gift sample from Wockhardt Pharmaceuticals, Aurangabad, India. Xanthan gum was procured from Krystal Colloid, Mumbai, India. HPMC K100M, HPMC K 15M, HPMC K4 M and Starch were supplied by Colorcon Asia Pvt, Ltd. MCC was supplied by Signet Chemical Corporation, Mumbai. Sodium bi carbonate and Magnesium stearate were supplied by Loba Chemicals, Mumbai. All the other chemicals and reagents used were of analytical grade.

Methods:

Characterization of drug:

Determination of melting point:

The melting point of Venlafaxine Hydrochloride was determined by capillary method.

Spectral analysis of Venlafaxine Hydrochloride

UV spectroscopy:

Preparation of Stock Solution- A of drug: 10 mg of drug was dissolved in 100 ml of 0.1 N HCl in the volumetric flask.1 ml stock solution A was taken and diluted by 0.1 N HCl in volumetric flask and scanned it in UV-spectrophotometer in the range of 200- 400 nm using 0.1 N HCl as blank and the λ max i.e. analytical wavelength was determined

Preparation of standard curve: From the stock solution A volume of solution of various concentrations i.e. 2, 4, 6, 8, 10, 12,14,16 and 18μg/ml were prepared using 0.1 N HCl to the

volume of 10ml in a volumetric flask. The absorbances were measured at analytical wavelength and a standard curve of Beer's law was plotted [13].

Infrared Spectroscopy: To detect any incompatibility of drug with polymer the IR spectroscopic analysis was carried out; the potassium bromide disc-containing drug and physical mixture of drug and polymer of batch F9 was prepared to record the spectrum in the range of 4000to 400 cm^{-1} by using FTIR Spectrophotometer.

Formulation development of sustained release layer: Sustained release layer contains the drug and other excipients as given in **Table 1**. The tablets were prepared by direct compression method. All ingredients were passed through sieve (100#) and mixed well in mortar. Weighed quantities of sustained release layer equivalent to 213 mg were compressed using a die of 9 mm.

TABLE 1: FORMULATION OF SUSTAINED RELEASE LAYER

Composition of sustained release layer							
Formulation Batches	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
Ingredients	**Weight in mg per tablet**						
Venlafaxine HCl	75	75	75	75	75	75	75
HPMC K4M	90	-	-	45	-	45	30
HPMC K15M	-	90	-	45	45	-	30
Xanthan gum	-	-	90	-	45	45	30
Starch	20	20	20	20	20	20	20
MCC	25	25	25	25	25	25	25
Magnesium stearate	3	3	3	3	3	3	3
Total wt.				213			

Formulation development of floating layer: All ingredients were passed through sieve (100#) and mixed well in mortar. Floating layer contains three ingredients such as sodium bicarbonate, HPMC K 100M, starch. Composition of floating layer is given in **Table 2**.

TABLE 2: FORMULATION OF FLOATING LAYER

Composition of floating layer			
Formulation Batches	**F8**	**F9**	**F10**
Ingredients	**Weight in mg per Tablet**		
Sodium bicarbonate	25	50	75
HPMC K 100 M	40	40	40
Starch	50	25	-
Total	**115**	**115**	**115**

Formulation of Bilayer floating tablets: Bilayer tablets contain the two layers i.e. floating layer and sustained release layer. Floating layer contains three ingredients and sustained release layer contains the drug and other excipients as mentioned in **Table 3**. The tablets were prepared by direct compression method.

TABLE3: FORMULATION OF BILAYER FLOATING TABLET

Composition of bilayer floating tablets			
Formulation Batches	**F8**	**F9**	**F10**
Ingredients	**Weight in mg per tablet**		
Release layer of optimized batch i.e. F7	213	213	213
Sodium bicarbonate	25	50	75
HPMC K 100 M	40	40	40
Starch	50	25	-
Total	328	328	328

All ingredients were passed through sieve (100#) and mixed well in mortar. Weighed quantities of SR layer equivalent to 213 mg (optimized batch i.e F7) were precompressed. Weighed quantities of floating layer equivalent to 115 mg add on the precompressed SR layer and both the layers were compressed in a die of 9 mm.

Evaluation of powder mixtures:

Bulk density: Bulk density is defined as a mass of a powder divided by the bulk volume. A sample powder of venlafaxine hydrochloride (05 gm) was introduced in 100 ml graduated cylinder. The volume of the material was noted on graduated cylinder. The bulk density was calculated by the formula given below [14-15].

$$\text{Bulk density } (\rho_0) = M/Vo$$

Where, M = mass of the powder and Vo = volume of the powder

Tapped Density: The powder sample under test was screened through sieve 18#, the weight of sample equivalent to 50 gm was filled in 100 ml graduated cylinder. The mechanical tapping of the cylinder was carried out at a rate of 300 drops per minute for 500 times from 3" height and the tapped volume Vf was noted [15].

The tapped density was calculated in gm/ cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = M/Vf$$

Where, M = weight of sample powder taken and Vf = tapped volume

Angle of repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation

$$\tan \theta = h / r$$

$$\text{Therefore; } \theta = \tan^{-1} (h / r)$$

Carr's index:

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

$$\% \text{ Compressibility} = \frac{D_o - D_f \times 100}{D_o}$$

Where, D_f = Fluff or Poured bulk or bulk density and D_o = Tapped or Consolidated bulk density.

Hausner ratio: Tap ped density and bulk density were measured and the Hausner ratio was calculated using the formula.

$$\text{Hausner ratio} = \rho t/\rho o$$

Where, ρt = tapped density and ρo = bulk density

Evaluation of tablets:

***In vitro* Evaluation:**

Tablet thickness and diameter:

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using digital vernier caliper [16].

Tablet hardness:

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2 [17].

Friability:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure.

Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined [17].

Uniformity of weight:

Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in table 9 and none deviates by more than twice that percentage.

Uniformity of content:
This test was applicable to tablets that contain less than 10 mg or less than 10 % w/w of active ingredient. Content of active ingredient in tablets, taken at random, was determined. Crush tablets and powder equivalent to weight of tablet dissolved in 0.1N HCl. Drug content was calculated by measuring absorbance at wavelength 225 nm. The tablet comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 % of the average value. If two or three of the individual values are outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 %, repeat the determination using another 20 tablets. The tablet comply with the test if in the total sample of 30 tablets not more than three of the individual values are outside the limits 85 to 115 % and none is outside the limits 75 to 125 % of the average value [17] .

Dissolution studies:
The release rate of Venlafaxine HCl from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37°C with 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly for 12 hrs and were replaced with fresh dissolution medium. The aliquots were filtered through Whatsman filter paper no. 41. Absorbance of these solutions was measured at 225 nm. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. Release studies were performed in triplicate [18].

Floating behavior: Floating behavior studies were performed on both the floating layer and Bilayer floating tablet, carried out in a USP Dissolution Testing Apparatus II (Paddle type) at paddle speed 50 rpm in 900ml 0.1 N HCl at 37 °C for 12 h to mimic in vivo conditions. To determine and optimized the floating lag time and buoyancy duration of the delivery system, 25, 35, 45, 55, 65 and 75mg gas generating salt mixtures were incorporated into the gas-generating layer while the weight of other formulation components were kept constant. Since it was known that the compression force applied to the tablet affects the onset time of floating, tablets were pressed first with different compression forces, with their effect on the onset time examined. The time interval between the introduction of the tablet into the dissolution medium and its buoyancy to the top of dissolution medium was taken as buoyancy lag time, the duration of system floatation and also the relative matrix integrity was observed visually.[19]

Floating lag time:
This test was performed in beaker containing 900 ml 0.1 N HCl as a testing medium maintained at 37^0C. The time required for the tablet to rise to the surface and float was determined as floating lag time [19].

Floating time:
Floating time was the time, the tablet floats in dissolution medium (including floating lag time) **[19].**

Model fitting:
The model fitting for percent cumulative release was done using PCP Disso software to find the best fitted kinetic equation for the dissolution profile.

Kinetics of drug release:
In order to understand the mechanism and kinetics of drug release, the results of the *in-vitro* dissolution study of the optimized batch of microspheres (batch) was fitted with various kinetic equations like.

i. Zero order (% release -K t),
ii. First order (log %Unreleased -Kt),
iii. Higuchi's model (%Release -$Kt^{0.5}$) and
iv. Pappas Korsmeyer Equation(% Release-Kt^n)

(Or) empirical equation (Power law expression) of

$$M_t / M_\infty = K t^n$$

Where,
M_t - amount of drug release at time t
M_∞ - amount of drug release at infinite time
K - constant characteristics, and
n - Diffusion exponent
If n - 0. indicates Fickian diffusion mechanism (Higuchi matrix) 5

n -0.5 to 1 indicates Anomalous Transport or Non Fickian transport.
n – 1 indicates Case II Transport (Zero order release)
n > 1 indicates Super case –II transport

Coefficient of correlation (R^2) values were calculated for the linear curves obtained by regression analysis of the above plots (Table No. 22 and 23) [20-22].

Accelerated stability studies:
In any rationale design and evaluation of dosage forms for drugs, the stability of the active component must be major criteria in determining their acceptance or rejection. During the stability studies the product is exposed to normal conditions of temperature and humidity. However the studies will take a longer time and hence it would be convenient to carry out the accelerated stability studies where the product is stored under extreme conditions of temperature. In the present study, stability studies were carried out on formulations F9. The tablets were stored at 40^0 C/75 ± 5 % RH for duration of one month. After thirty days each sample was withdrawn and tested for drug content, floating lag time and drug release study [23].

RESULT AND DISCUSSION:

Selection of excipients:
Rational behind selection of excipients is given in the **Table 4**.

TABLE 4: SELECTION OF EXCIPIENTS

Sr. No.	Ingredients	Functional Category
1	HPMC K 15 M	Hydrophilic SR polymer
2	HPMC K 4 M	Hydrophilic SR polymer
3	Xanthan gum	Sustained release agent
4	Microcrystalline cellulose	Diluent
5	Starch	Binder
6	Sodium bicarbonate	Gas generating agent
7	Magnesium stearate	Lubricant

Characterization of drug
Determination of melting point: The uncorrected value for melting point is 210-214°C. The reported melting point values for Venlafaxine HCl are in the range of 216°C. The slight deviation observed in the values may be due to differences in the experimental conditions.

Spectral analysis of Venlafaxine HCl:

a) UV spectroscopy: The UV spectrum of Venlafaxine HCl indicates the value for λ_{max} as 225 nm. The spectrum is shown **in Fig. 1, 2**.

TABLE 5: CALIBRATION CURVE FOR VENLAFAXINE HCL IN 0.1N HCL

Sr. No.	Concentration µg/ml	Absorbance
1	0	0
2	2	0.074
3	4	0.145
4	6	0.232
5	8	0.297
6	10	0.363
7	12	0.449
8	14	0.531
9	16	0.592

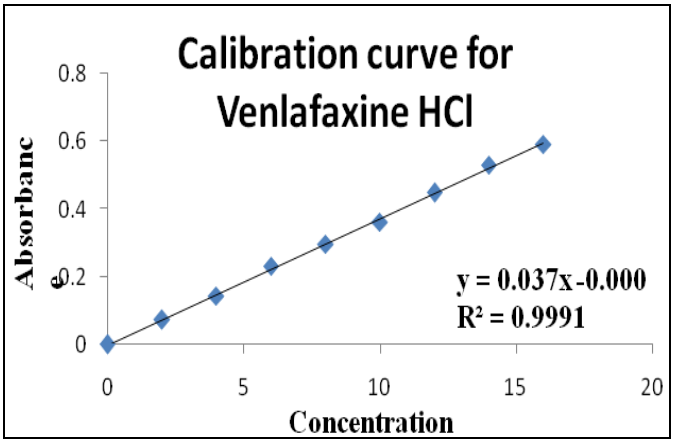

FIG.1: CALIBRATION CURVE FOR VENLAFAXINE

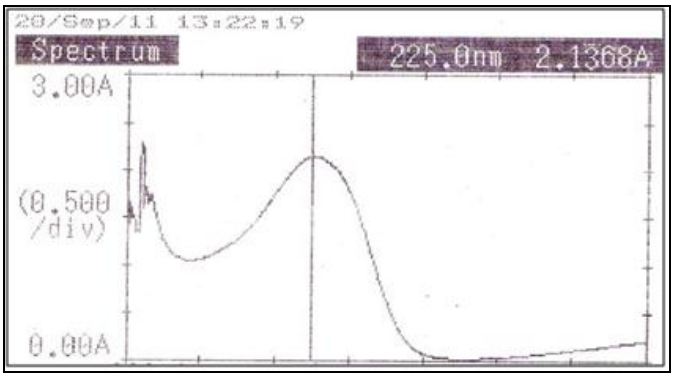

FIG.2: UV SPECTRUM OF VENLAFAXINE HCL

Venlafaxine HCl showed maximum absorption at wavelength 225 nm in 0.1 N HCl. Calibration curve was done by taking absorption of diluted stock solutions at wavelength 225 nm. Resuls are tabulated in **Table 5**.

b) Infrared spectroscopy: From the combined spectral data **(Fig .3 and Fig.4)** and functional group analysis it can be concluded that given sample is of the drug Venlafaxine.

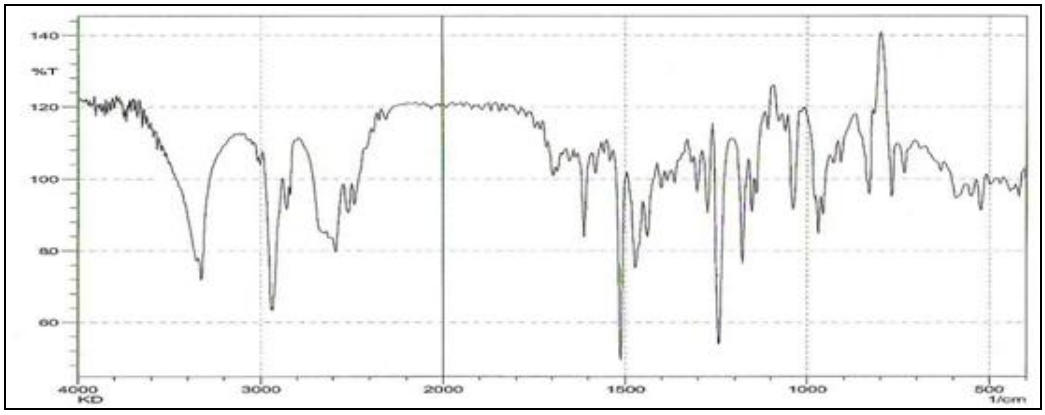

FIGURE 3: IR SPECTRUM OF VENLAFAXINE HCL

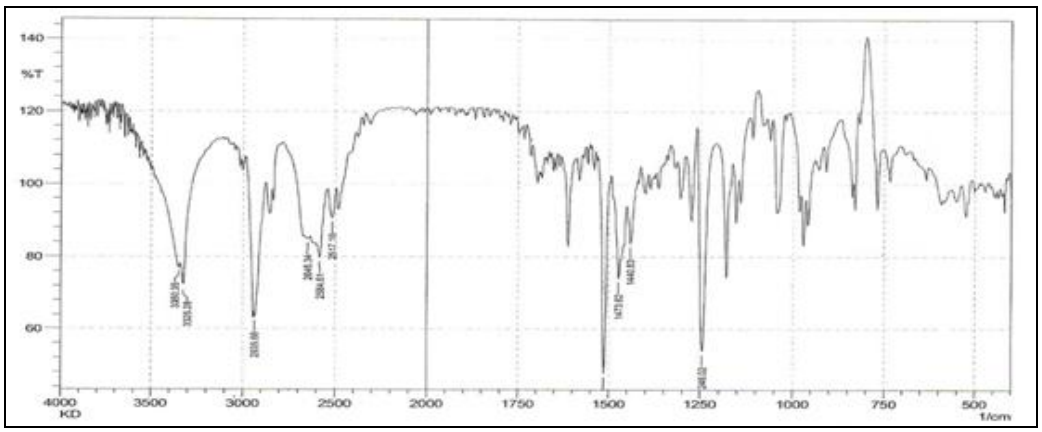

FIG. 4: IR SPECTRUM OF SAMPLES; – PURE DRUG, HPMC K 15 M, HPMC K 4 M, HPMC K 100 M, AND XANTHAN GUM

Tablet of Batch F9 did not show any physical or chemical interaction between drug and polymer. Which was concluded from the IR Study showed similar peak of drug in tablet formulation.

Formulation development of sustained release layer: The Sustain release layer provided Sustain release of active material and contains drug, HPMC K 4 M and HPMC K 15 M as a hydrophilic matrix material. Starch was used as filler – binder and MCC was added as diluent. Improving the retardation of the drug release form the matrices, keeping the aim, further attempt was made using combination of HPMC's with Xanthan Gum. Xanthan Gum was added as the release rate retardant. Xanthan Gum is classified under the group of natural gum which has good gel-forming property.

Evaluation of powder mixtures:

TABLE 6: BLEND PROPERTIES OF SUSTAINED RELEASE LAYER TABLET FORMULATIONS

Formulations	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose	Carr's Index	Hausner ratio
Venlafaxine HCl	0.3846 ± 0.01	0.4347 ± 0.02	45°47' ± 0.11	11.53 ± 0.12	1.13 ± 0.015
F1	0.4 ± 0.02	0.4629 ± 0.01	28°42 ±0.31	13.6 ± 0.02	1.15 ± 0.015
F2	0.3846 ± 0.04	0.4347 ± .02	28 °19' ± 0.17	11.53 ± 0.04	1.13 ± 0.03
F3	0.4 ± 0.01	0.4464 ± 0.03	28°85' ± 0.28	10.4 ± 0.05	1.11 ± 0.02
F4	0.4 ± .02	0.4545 ± 0.03	30°73' ± 0.12	12 ± 0.12	1.13 ± 0.025
F5	0.4166 ± 0.05	0.4761 ± 0.02	30°14' ± 0.24	12.5 ± 0.05	1.14 ± 0.035
F6	0.3937 ± 0.02	0.4716 ± 0.02	30°52' ± 0.16	16.53 ± 0.14	1.19 ± 0.02
F7	0.4 ± 0.02	0.4761 ± 0.01	29°67' ± 0.28	16 ± 0.13	1.19 ± 0.015

* Each sample was analyzed in triplicate (n = 3)

The physical characterization of the sustained release layer was done by evaluating them for the physical characteristics such as bulk density, tapped density, angle of repose, Carr's index, Hauser's ratio. It was found to be 0.3846 ± 0.01 to 0.4166 ± 0.05gm/cm^3, 0.4347 ± 0.02 to 0.4761 ± 0.02gm/cm^3, 28°19' ± 0.17 to 45°47 ± 0.28, 10.4 ± 0.05 to 16.53 ± 0.14, 1.11 ± 0.02 to 1.19 ± 0.02 respectively from **Table 6**. It was found that the bulk density, tapped density, angle of repose, Carr's index and Hauser's ratio for Sustained release layer indicate good flow property.

Evaluation of tablets:

A. *In vitro* evaluation:

TABLE 7: EVALUATION OF TABLETS OF SUSTAINED RELEASE FORMULATION

Formulation	Diameter (mm)	Thickness (mm)	Hardness (kg/cm2)	% Friability
F1	9.02± 0.15	2.1± 0.06	6.6± 0.05	0.428± 0.11
F2	9.04± 0.11	2.0± 0.08	6.4± 0.06	0.422± 0.08
F3	9.02± 0.16	2.1± 0.04	6.0± 0.05	0.418± 0.12
F4	9.04± 0.28	2.0± 0.06	6.4± 0.06	0.452± 0.08
F5	9.05± 0.14	2.3± 0.04	6.3± 0.04	0.454± 0.06
F6	9.04± 0.22	2.0± 0.09	6.0± 0.06	0.444± 0.08
F7	9.01± 0.18	2.2± 0.06	6.4± 0.04	0.453± 0.10

* Each sample was analyzed in triplicate (n = 3)

Tablet thickness and diameter:

From **Table 7** we can say that thickness of the formulations F1 to F7 varied from 2.0 ± 0.06 to 3.4 ± 0.06 mm and diameter of the formulations F1 to F7 varied from 9.01 ± 0.18 to 9.05 ± 0.14 mm. Size of dosage unit also affects the gastric emptying. The diameter of the dosage unit is also equally important as a formulation parameter. Timmerm ans and Andre et al studied the effect of size of floating and nonfloating dosage forms on gastric emptying and concluded that the floating units remained buoyant on gastric fluids. The floating dosage forms are more often emptied from the stomach before the on floating ones, which lie in the antrum region and are propelled by the peristaltic waves. However, the nonfloating dosage form never show very prolonged GRTs and both types of forms are better retained as their size increases[23].

Tablet hardness:

From **Table 7** we can say that hardness of tablets of each formulation was measured and found in the range of 6.0 ± 0.05 to 6.6 ± 0.05kg/cm^2. Each sample was analyzed in triplicate. A difference in tablet hardness reflects differences in tablet density and porosity, which are supposed to result in difference release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet and formation of the gel barrier. Therefore, such an effect is expected to be prominent during the initial phase of the dissolution curve. However the results reported until now by many researcher suggested that tablet hardness has no or little effect on the release profile; this can be attributed to the fact that variations in the release pattern as a result of differences in tablets density and porosity during the initial period of dissolution could possibly be diminished by high affinity of the HPMC to the aqueous solution.

Friability:

From Table 13.we can say that percentage weight loss of the tablets of each formulation was measured and found to be in the range of 0.418 ± 0.12 to 0.454 ± 0.06%. Each sample was analyzed in triplicate (n = 3).

Uniformity of weight:

Tablets from each batch showed uniformity of weight as per IP limits.

Uniformity of content:

Tablets from each batch showed uniformity of content as shown **Table 8**.

TABLE 8: UNIFORMITY OF CONTENT

Formulation Batches	Uniformity of content (%)
F1	98.89± 0.48
F2	99.22± 0.77
F3	99.92± 0.64
F4	98.78± 0.38
F5	99.96±0.46
F6	99.84±0.54
F7	99.08± 0.87
F8	99.48±0.42
F9	98.98±0.42
F10	98.98±0.42

Dissolution studies:

Venlafaxine HCl release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. Average percentage drug release of sustain release layer from batch F1 to batch F4 is shown in **Table 9**.

TABLE 9: *IN-VITRO* DISSOLUTION DATA OF BATCH F1 TO F4

	Cumulative % drug release			
Time (Hr)	**Batch F1**	**Batch F2**	**Batch F3**	**Batch F4**
0	0	0	0	0
1	24.94 ± 1.03	30.27 ± 1.17	38.31 ± 1.66	29.95 ± 1.46
2	30.18 ± 1.21	42.69 ± 1.45	54.57 ± 1.42	32.13 ± 1.22
3	35.76 ± 1.56	48.28 ± 1.62	65.78 ± 1.53	36.25 ± 1.41
4	39.86 ± 1.44	58.55 ± 1.44	70.95 ± 1.47	46.23 ± 1.37
5	46.47 ± 0.98	62.34 ± 1.45	80.37 ± 1.26	49.12 ± 1.08
6	48.66 ± 1.35	66.04 ± 1.62	89.01 ± 1.10	60.93 ± 1.31
7	51.78 ± 1.10	66.91 ± 1.44	90.05 ± 1.10	64.47 ± 1.42
8	55.05 ± 1.32	70.13 ± 1.07	92.78 ± 1.26	66.33 ± 1.24
9	57.47 ± 1.06	73.76 ± 1.29	95.61 ± 1.10	71.29 ± 1.62
10	64.09 ± 1.52	75.15 ± 1.68	98.26 ± 1.10	74.63±1.12
11	71.36 ± 0.96	75.98 ± 1.24	------	75.12±1.12
12	77.89 ± 1.26	76.08± 1.03	------	75.98±1.12

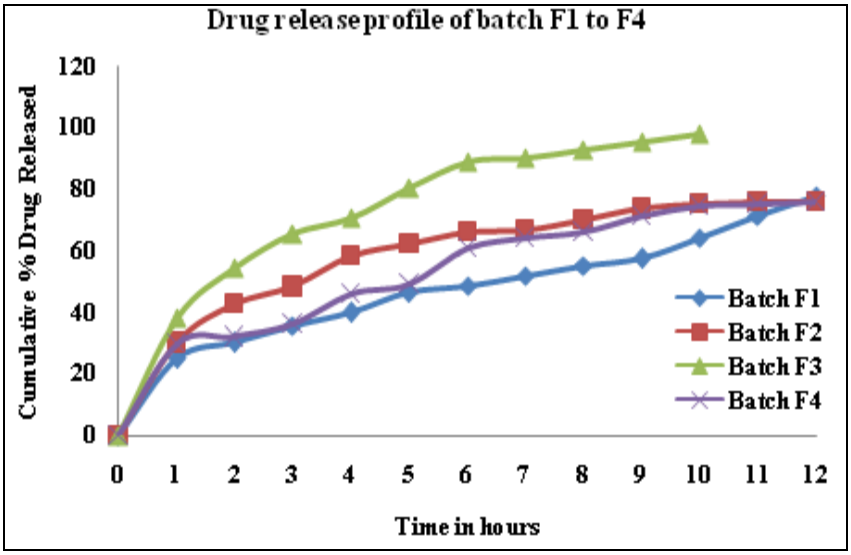

FIG. 5: DRUG RELEASE PATTERN OF HPMC K 4 M, HPMC K 4 M AND XANTHAN GUM BATCHES

The results of dissolution studies of formulations F1 composed of HPMC K 4 M, formulations F2 composed of HPMC K 15 M and formulations F3 composed of Xanthan gum prepared by direct compression technique. **Table 9** shows the data of drug release from the hydrophilic matrices. Formulation F3 disintegrated within 10hr. Drug release in approximately 77.89 ± 1.26 %, 76.08± 1.03% and 98.26 ± 1.10 %, 75.98 ±1.12 respectively, while formulations F1, F2, F4 were able to retard the release over 12 hrs. **Fig.5** shows the Venlafaxine HCl percentage drug release graphed versus time for the formulations.

TABLE 10: *IN-VITRO* DISSOLUTION DATA OF BATCH F5 TO BATCH F7.

	Cumulative % drug release		
Time in hours	**Batch F5**	**Batch F6**	**Batch F7**
0	0	0	0
1	33.71± 1.12	46.48± 1.34	23.38± 1.46
2	48.19± 0.99	56.75 ± 1.23	28.55± 1.14
3	57.10± 1.21	64.02± 1.08	35.83± 0.96

4	70.71± 1.34	67.07± 1.46	41.80± 1.38
5	74.70± 0.96	70.23± 1.16	50.53± 1.16
6	80.52± 1.32	76.85± 1.52	60.51± 1.35
7	84.86± 1.44	80.58± 1.28	72.11± 1.24
8	89.66± 1.64	83.48± 1.64	79.82± 1.22
9	90.01± 1.38	86.38± 1.22	83.65± 1.06
10	92.36± 1.15	90.49± 1.16	87.01± 1.21
11	93.23± 1.26	95.96± 1.45	91.51± 1.06
12	93.36± 1.26	------	97.47± 1.06

Average percentage drug release of sustained release layer from batch F7 to batch F9 is shown in **Table 10**. The results of dissolution studies of formulation F5 composed of HPMC K 15 M, xanthan gum and formulation F6 composed of HPMC K 4 M, xanthan gum and formulation F7 composed of combination of HPMC K 4 M, HPMC K 15 M and xanthan gum. Tablet formulation F6 showed 95.96 ± 1.45 % drug release within 11 hr., while F5 and F7 showed 93.36 ± 1.26 % and 97.47 ± 1.06 % drug release within 12 hr. Formulation F5 and F7 retard drug release up to 12 hr. but batch F5 not achieve the $t_{95\ \%}$. **Fig. 6** shows the percentage drug release from HPMC K 15 M, HPMC K 4 M, xanthan gum combination batches.

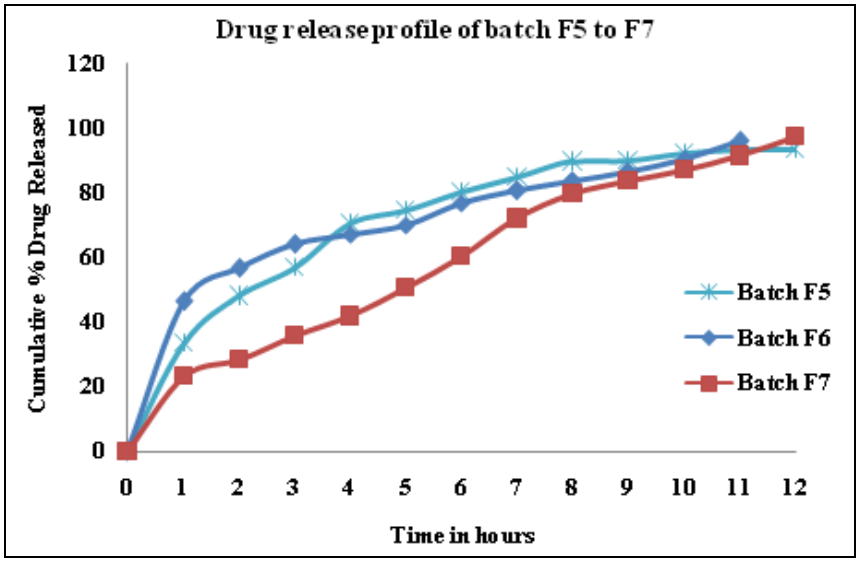

FIG.6: DRUG RELEASE PATTERN OF BATCH F5 TO F7 SHOWING RELEASE FROM HPMC K 15 M, HPMC K 4 M, AND XANTHAN GUM COMBINATION BATCHES.

HPMC is a hydrophilic polymer that swells to a significant extent upon contact with water. Depending on its degree of substitution and on its molecular weight, it dissolves more or less rapidly. An increase in the polymer concentration, induce a decrease in the release rate. High concentration of HPMC resulting in the more gel formation and forms a gelatinous barrier, which may retard the drug release in the formulations.

Being obvious, HPMC K 15 M showed better retardation than HPMC K 4 M. As expected, the drug release rate was found to be dependent on the viscosity grade and the concentration of polymer used. Marianne oth and et al studied that an increase in the HPMC viscosity a decreased in release rate was observed. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation of drug release. Xanthan gum shows better sustained release action in combination with HPMC – K 15 M and HPMC – K 100 M.

Preparation of floating release tablets:

Various floating layer formulations were formulated with HPMC – K 15 M and HPMC – K 100 M polymer alone. HPMC K – series has the fastest rate of hydration compared to E and F series due to the hydrophobic and hydrophilic substituents i.e. methoxyl group and hydroxylpropyl group on

it. The different viscosity grades of the same polymer displayed significant difference in the floating capabilities. HPMC – K 100 M showed better floating capabilities compared to HPMC – K 15 M, which may be due to greater molecular weight than HPMC – K 15 M and good gel forming capability of it with starch. Sodium bicarbonate was added as a gas-generating agent. The ideal amount of both, effervescent mixture and polymer, for the floating layer were estimated by determining onset time of floating. In an attempt to shorten the onset time by increasing the concentration of effervescent mixture, it was observed that tablets were dispersed; on the other hand, lower concentration cause this duration to prolong. In bilayer tablets sodium bicarbonate incorporated in separate layer so less concentration (50.0 mg) of sodium bicarbonate was required. Starch was added as binder. Starch helps in forming gel with HPMC K 100 M and retaining the air bubbles formed from sodium bicarbonate to provide floating ability.

Table 11 shows the bulk density, tapped density, Percent compressability, Carr's index and Hauser's ratio for floting layer indicate good flow property.

Evaluation of powder mixtures of floating layer:

TABLE 11: MICROMERITICS CHARACTERIZATION

Formulation Batch	Bulk density (gm/cm3)	Tap density (gm/cm3)	% compressibility index	Hausner's ratio	Angle of Repose
F8	0.4065 ± 0.03	0.4716 ± 0.03	13.12 ± 0.8	1.16 ± 0.015	26°25'
F9	0.3937 ± 0.02	0.4347 ± 0.05	9.44 ± 0.07	1.10 ± 0.035	27°35'
F10	0.3816 ± 0.03	0.4545 ± 0.04	16.03 ± 0.14	1.19 ± 0.035	29°25'

Floating behaviour:

From the results of floating behavior studies, it was found that as the concentration of effervescent mixture increased, the floating lag time, floating duration decreased and vice versa. A reverse trend was observed on increasing the polymer concentration. As dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of carbon dioxide gas within the swollen gel thus causing floatation as the matrix volume expanded and its density decreased. Therefore the concentration of the effervescent mixture was chosen so as not to compromise the matrix integrity with the possible shortest lag time and floating duration upto 12h. It was observed that all the tablets ascended to the upper one third of the dissolution vessels within a short time, and remained floated until the completion of release studies.

Floating lag time:

TABLE 12: FLOATING LAG TIME OF FORMULATIONS

Formulation Batch	Floating lag time (Sec.)
F8	400± 0.05
F9	70± 0.02
F10	62± 0.07

Floating time:

Floating time was found to be dependent on HPMC content. HPMC was a swelling polymer and degree of gelling and gel strength determines its buoyancy. Floting lag time for all the batches F8 to F10 are tabulated in table **Table 12** and shows the floating time more than 12 Hr.

Zhenping Wei and *et al*: reported that on contact with the dissolution medium hydrocolloid in the dissolution medium hydrocolloid in the test medium reacted with sodium bicarbonate from tablet inducing CO_2 formation in the tablets. Because the gas generated was trapped in and protected by gel formed by the hydration of HPMC.

This expansion keeps the whole tablet buoyant on the surface of test medium as long as possible. Each sample was analyzed in triplicate. Floating release tablet showed floating time over 12 hrs.

Preparation of Bilayer floating tablets:

Batch F7 was satisfying the t95 in preliminary studies so that batches are selected for preparation Bilayer floating tablet.

***In vitro* evaluation:**

TABLE 13: EVALUATION OF BILAYER FLOATING TABLET FORMULATIONS

Formulations Batches	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
F8	9.04 ± 0.15	3.3 ± 0.05	6.7 ± 0.05	0.434 ± 0.14
F9	9.04 ± 0.12	3.0 ± 0.08	6.6 ± 0.05	0.434 ± 0.14
F10	9.06 ± 0.09	3.1 ± 0.06	6.6 ± 0.03	0.434 ± 0.14

Evaluation characteristics of Bilayer floting tablets are shown in **Table 13**.

Tablet thickness and diameter: Thickness and Diameter of the formulations F8, F9 and F10 varied from 3.1, 3.0 and 3.1 mm and 9.04, 9.04 and 9.06 mm.

Tablet hardness: Hardness of tablets of each formulation was measured and found in the range of 6.6 to 6.7 kg/ cm^2. Each sample was analyzed in triplicate.

Friability: Percentage weight loss of the tablets of formulation was measured and found to be 0.463 and 0.478 %.

Uniformity of weight: Tablets from each batch showed uniformity of weight as per IP limits.

Uniformity of content: Tablets from each batch showed uniformity of content.

Dissolution study: As per the properties of gum used and polymer used following release was observed. Dissolution study data of Bilayer tablets are tabulated in **Table 14**.

TABLE 14: DISSOLUTION STUDY OF BILAYER TABLET FORMULATIONS

	Cumulative % drug released		
Time hours	Batch F8	Batch F9	Batch F10
0	0	0	0
1	32.18 ± 1.04	22.10 ± 0.66	26.63 ± 0.66
2	38.18 ± 1.42	28.43 ± 1.08	33.26 ± 1.08
3	41.63 ± 1.22	34.77 ± 0.84	40.79 ± 0.84
4	48.61 ± 0.86	41.72 ± 0.92	48.12 ± 0.92
5	51.95 ± 0.74	51.31 ± 1.26	54.62 ± 1.26
6	56.62 ±1.28	60.99 ± 0.84	58.64 ± 0.84
7	64.15 ± 0.82	70.74 ±0.92	67.04 ± 0.92
8	69.69 ±1.04	79.59 ± 1.26	69.87 ± 1.26
9	73.54 ±1.28	85.28 ± 1.41	74.44 ± 1.41
10	81.04 ± 0.82	89.66 ± 1.29	83.03 ± 1.29
11	86.92 ±1.04	93.52 ± 1.04	93.20 ± 1.04
12	90.11 ± 0.82	97.19 ± 1.16	96.25 ± 1.16

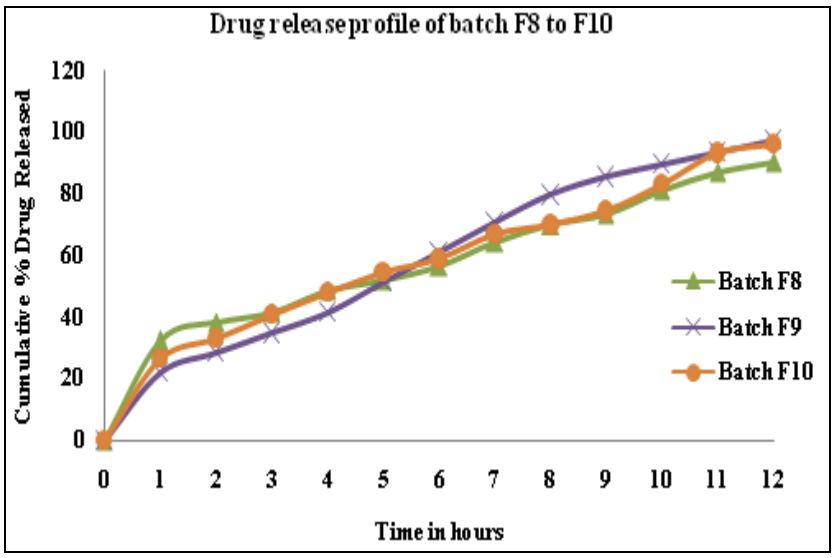

FIG.7: DISSOLUTION STUDY OF BILAYER TABLET FORMULATIONS

From the graph **Fig. 7** batch F9 was satisfying $t_{95\ \%}$ in 12 hr.

Release Kinetics:

TABLE 15: KINETIC DATA OF VENLAFAXINE HCL RELEASE LAYER TABLET

Formulation Batches	Zero order	First order	Matrix Model	Kosymer-Peppas model	Hixson Crowell Model
	R^2 values				
F1	0.887	0.8871	0.9884	0.9834	0.8871
F2	0.6438	0.6441	0.9752	0.9909	0.644
F3	0.7409	0.7413	0.9859	0.9926	0.7412
F4	0.8496	0.8497	0.9917	0.9743	0.8497
F5	0.7096	0.7099	0.9822	0.9887	0.7098
F6	0.7805	0.7808	0.9929	0.9905	0.7807
F7	0.9731	0.9732	0.9715	0.9847	0.9732

TABLE 16: KINETIC DATA OF VENLAFAXINE HCL RELEASE LAYER TABLET

Formulation Batches	Zero order	First order	Matrix Model	Kosymer-Peppas model	Hixson Crowell Model
	R^2 values				
F8	0.8858	0.886	0.9886	0.9718	0.886
F9	0.9733	0.9733	0.9717	0.9874	0.9733
F10	0.9384	0.9385	0.9869	0.9896	0.9385

Kinetic data of Vanlafaxin HCl release layer tablet were tabulated in **Table 15 and 16**. As observed from **Table 16**, the values of correlation coefficients (R^2) for all formulations were high enough to evaluate the drug dissolution behavior.

The values of release of exponent (n) were found to be a function of retardant polymer used and physico-chemical nature of drug. The values of release exponent (n), kinetic rate constant (k) and correlation coefficient (R^2) as calculated are shown **Table17.**

TABLE 17: ESTIMATED VALUES OF N AND K BY REGRESSION OF LOG (M_T / M_∞) ON LOG (T)

Formulation code	n	K	(R^2)	Best Fit Model
F1	0.4629	0.0047	0.9884	Matrix
F2	0.3904	0.0091	0.9909	Peppas
F3	0.4208	0.01	0.9926	Peppas
F4	0.4602	0.0054	0.9917	Matrix
F5	0.4357	0.0084	0.9887	Peppas
F6	0.4142	0.0092	0.9929	Matrix
F7	0.6186	0.0022	0.9847	Peppas
F8	0.4437	0.0064	0.9886	Matrix
F9	0.6725	0.0017	0.9874	Peppas
F10	0.5458	0.0035	0.9896	Peppas

From **Table 17**, it was observed that the best fitting linear parameter for formulation F1, F5, F7, F8, F9 and F10 was that of Higuchi Matrix model. This indicates that the drug release is controlled by diffusion of drug through the pores. Formulation F2, F3, F4 and F6 formulation were best fitted in Korsmeyer-Peppas model. This indicates that the release mechanism is not known or more than one type of release phenomenon could be involved.

TABLE 18: n VALUE AND RELEASE FOR KORSMEYER-PEPPAS MODEL

n	Mechanism
0.5	Fickian diffusion (Higuchi matrix)
0.5 < n < 1	Non-Fickian diffusion
1	Case II transport
>1	Super Case II transport

Table 18 n values and various release mechanism are shown.

In the present study, mean diffusional exponent values (n) for formulation F1-F9 were found to be ranged from 0.3181 to 0.4426 indicating all the formulation follows Fickian diffusion (Higuchi matrix) and formulation F10 was found to be 0.5021 indicating formulation follows Anomalous (Non-Fickian) transport.

Accelerated stability study:

The stability studies were carried out on optimizes formulation i.e. F9. The formulations were stored at 40^0C/75 % RH for a month. After 30 days samples

were withdrawn and retested for drug content, floating lag time and drug release studies. It indicates that irrespective of concentration of polymer, these formulations are able to retain their stability for a month.

Drug content and floating lag time of Bilayer tablet formulations after 30 days are shown in Table19 and dissolution studies are shown in **Table 20**.

TABLE 19: DRUG CONTENT AND FLOATING LAG TIME OF BILAYER TABLET FORMULATIONS

Formulation	Drug content (%)	Floating lag time (sec)
Initial	98.98 ± 0.54	70 ± 0.06
1 Month stability	97.50 ± 0.66	75 ± 0.08

Dissolution study:

TABLE 20: *IN-VITRO* RELEASE STUDY OF FORMULATION F9 BEFORE AND AFTER STABILITY STUDY

Cumulative % drug released		
Time (Hr)	**Initial**	**1 Month stability**
0	0	0
1	22.10 ± 1.06	21.97± 0.46
2	28.43± 1.12	28.27± 0.39
3	34.77± 1.34	34.71± 1.32
4	41.72± 0.66	41.46.± 1.46
5	51.31± 1.08	51.08± 0.68
6	60.99 ± 0.84	60.83± 0.96
7	70.74± 0.92	70.52± 1.30
8	79.49± 1.26	79.36± 1.28
9	85.28± 1.41	85.22.± 1.10
10	89.66± 1.29	89.46 ± 0.84
11	93.52± 1.04	92.39 ± 1.24
12	97.19± 1.16	96.12± 1.65

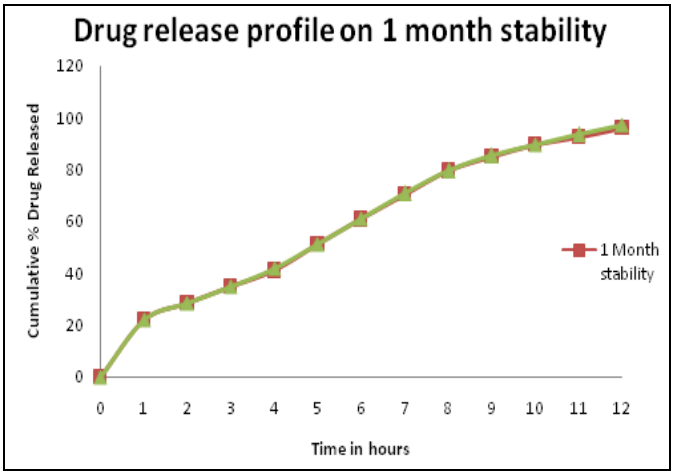

FIG.8*: IN-VITRO* RELEASE STUDY OF FORMULATION F9 AFTER STABILITY STUDY

From the **Fig. 8**, overlapping graphs were observed which indicate that there is not significant variation in dissolution profile for considerable period of time at adverse condition. Even at initial reading slight decrease in release was observed but after 12 hr batch is showing more than 95 % showing good stability.

CONCLUSION: The present study was carried out to develop the floating drug delivery with sustain release of Venlafaxine HCl using HPMC, K-grade polymer as a carrier and thereafter formulating the optimized formulation in combination with Xanthan gum. Friability, uniformity of content and weight variation of tablets complied with IP limit. Floating lag time of tablets depends on concentration of sodium bicarbonate and type and concentration of polymer. As concentration of sodium bicarbonate and polymer was increased, the floating lag time was decreased. Use of high viscosity polymer can also decrease floating lag time but, the use of high viscosity polymer increases the matrix integrity and resultant weight of tablets.

Concentration and viscosity of polymer should be directly proportional with swelling characteristics of tablets. In dissolution study of all formulations it was observed that by increasing concentration of polymers and increasing viscosity of polymers, release rate of drug was retarded. Bilayer tablets showed more floating lag time and more uniformity in drug release rate. Increase in bioavailability was also observed which shows that there is a need of Venlafaxine HCl in floating drug delivery system.

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