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Design and Characterization of Effervescent Gastro Retentive Floating Tablets by Using Venlafaxine Hcl as a Model Drug

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Abstract: *In the present research work the gastro retentive floating matrix formulation of Venlaflaxine hydrochloride by using various hydrophillic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC and Guar gum. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Guar gum were in the concentration of 120mg (F4) showed maximum drug release 99.76% in 12 hours with good floating lag time and duration of floating.The formulations prepared with HPMC K 15 M retarded the drug release up to 12 hours in the concentration of 120 mg (F8).The formulations prepared with HPMC K100M were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics; from the release kinetics data it was evident that the formulation followed peppas mechanism of drug release.*

Keywords: *Venlaflaxine hydrochloride, HPMC polymers, Floating tablets.*

I. Introduction

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process.

In order to overcome the drawbacks of conventional drug deliver systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits .

1.1 Gastro Retentive Dosage Form (Grdf)

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS).

GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as –

1) This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastro retentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2) GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the sub mucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).

1.2 Approaches To Gastric Retention

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include: Floating systems, Bio adhesive systems, swelling and expanding systems, High density systems, Modified systems

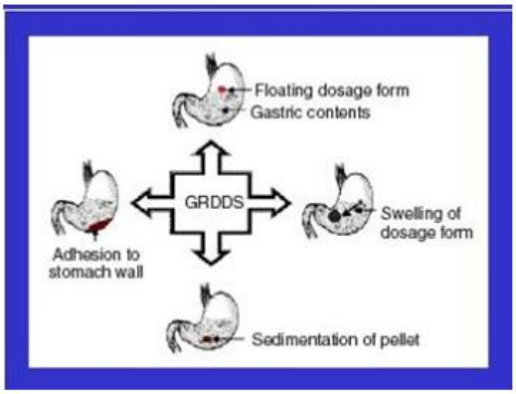

Fig: Classification of gastro retentive drug delivery system

1 Buoyant/ Floating Systems
2 Bio/Muco-adhesive Systems
3 Swelling and Expanding Systems
4 High Density Systems
5 Incorporation of Passage Delaying Food Agents
6 Ion Exchange Resins
7 Osmotic Regulated Systems

1.3 TYPES OF FLOATING DRUG DELIVERY SYSTEMS (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are:

A. Effervescent System, and
B. Non- Effervescent System.

1.3.1. EFFERVESCENT SYSTEM

Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO_2) gas, thus reducing the density of the system and making it float on the gastric fluid. An alternative is the incorporation of matrix containing portion of liquid, which produce gas that evaporates at body temperature.
These effervescent systems further classified into two types.

I. Gas Generating systems
II. Volatile Liquid/Vacuum Containing Systems.

1.3.2. NON-EFFERVESCENT SYSTEMS

The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. The most commonly used excipients in non-effervescent FDDS are gel forming or highly swellable cellulose type hydrocolloids, polysaccharides and matrix forming material such as Polycarbonate, Polyacrylate, Polymethacrylate, polystyrene as well as bioadhesive polymer such as Chitosan and Carbopol. The various types of this system are as:

1 Single Layer Floating Tablets
2 Bilayer Floating Tablets
3 Alginate Beads

ADVANTAGES OF FDDS

Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.

DISADVANTAGES OF FDDS

1. Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
2. Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.
3. High variability in gastric emptying time due to its all or non-emptying process.

II. Materials

Name of the material
Venlafaxine hydrochloride
Hydroxy Propyl Methyl Cellulose grades
Guar gum
Sodium bicarbonate
Magnesium stearate
Micro crystalline cellulose
Talc

III. Methodology

3.1 ANALYTICAL METHOD DEVELOPMENT

DETERMINATION OF ABSORPTION MAXIMA

A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

PREPARATION CALIBRATION CURVE

100mg of Venlaflaxine HCl pure drug was dissolved in 100ml of water(stock solution)10ml of solution was taken and make up with100ml of water (100µg/ml).from this 10ml was taken and make up with 100 ml of water (10µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of Venlaflaxine HCl per ml of solution. The absorbance of the above dilutions was measured at 225 nm by using UV-Spectrophotometer taking 0.1N HCl as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis.

3.2. DRUG – EXCIPIENT COMPATIBILITY STUDIES

FOURIER TRANSFORMS INFRARED (FTIR) SPECTROSCOPY

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

3.3. PREFORMULATION PARAMETERS

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

ANGLE OF REPOSE

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was calculated using the following formula;

$\tan \theta = h / r$

$\tan \theta$ = Angle of repose, h = Height of the cone , r = Radius of the cone base

BULK DENSITY

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3.

The bulk density was calculated using the formula;

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample, V_o = apparent volume of powder

TAPPED DENSITY

The tapped density was calculated, in gm per L, using the formula;

$$Tap = M / V$$

Where, Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

MEASURES OF POWDER COMPRESSIBILTY

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities

Compressibility Index was calculated using the following formulas;

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

Where, b = Bulk Density, Tap = Tapped Density

HAUSNER RATIO

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula;

$$\text{Hausner's Ratio} = \text{Tapped density} / \text{Bulk density}$$

3.4 FORMULATION DEVELOPMENT OF TABLETS

All the formulations were prepared by direct compression. The compression of different formulations are given in Table 6.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Venlaflaxine Hydrochloride. Total weight of the tablet was considered as 300mg.

PROCEDURE

1) Venlaflaxine HCl and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

OPTIMIZATION OF SODIUM BICARBONATE CONCENTRATION

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the concentration of sodium bicarbonate was finalized and preceded for further formulations.

TABLE: Optimization sodium bicarbonate concentration

S.No	Excipient Name	F1	F2	F3
1	Venlafaxine	75	75	75
2	HPMC K 100M	100	100	100
3	$NaHCO_3$	25	50	75
4	Mg.Stearate	5	5	5
5	Talc	5	5	5
6	MCC pH 102	90	65	40

All the quantities were in mg Based on the floating lag time and floating duration the concentration of sodium bicarbonate was optimised.

TABLE : Formulation Composition For Floating Tablets

FORMUATION NO.	VENLAFAXINE HCL	GAUR GUM	HPMC K15	HPMC K100	NAHCO3	MAG. STEARATE	TALC	MCC PH 102
F1	**75**	**30**			**50**	**5**	**5**	**135**
F2	**75**	**60**			**50**	**5**	**5**	**105**
F3	**75**	**90**			**50**	**5**	**5**	**75**
F4	**75**	**120**			**50**	**5**	**5**	**45**
F5	**75**		**30**		**50**	**5**	**5**	**135**
F6	**75**		**60**		**50**	**5**	**5**	**105**
F7	**75**		**90**		**50**	**5**	**5**	**75**
F8	**75**		**120**		**50**	**5**	**5**	**45**
F9	**75**			**30**	**50**	**5**	**5**	**135**
F10	**75**			**60**	**50**	**5**	**5**	**105**
F11	**75**			**90**	**50**	**5**	**5**	**75**
F12	**75**			**120**	**50**	**5**	**5**	**45**

All the quantities were in mg , total weight is 300 mg.

3.5. EVALUATION OF POST COMPRESSION PARAMETERS FOR PREPARED TABLETS

The designed formulation compression coated tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

WEIGHT VARIATION TEST

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

HARDNESS

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

THICKNESS

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

FRIABILITY

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W1] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

3.6 DETERMINATION OF DRUG CONTENTS

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of venlaflaxine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

3.7 IN VITRO BUOYANCY STUDIES

The in vitro buoyancy was determined by floating lag time, and total floating time. (As per the method described by Rosa et al) The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and duration of time the tablet constantly floats on the dissolution medium was noted as Total Floating Time respectively (TFT).

INVITRO DRUG RELEASE STUDIES DISSOLUTION PARAMETERS:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCl
RPM	--	75
Sampling intervals (hrs)	--	ss 0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c $\pm$ 0.5°c

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

PROCEDURE

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 12 hours and then the medium 0.1 N HCl was taken and process was

continued from 0 to 12 hrs at 75 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 271 nm using UV-spectrophotometer.

3.8 APPLICATION OF RELEASE RATE KINETICS TO DISSOLUTION DATA

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

ZERO ORDER RELEASE RATE KINETICS

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

FIRST ORDER RELEASE RATE KINETICS

The release rate data are fitted to the following equation

$\text{Log } (100\text{-}F) = kt$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

HIGUCHI RELEASE MODEL

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$F = k\ t1/2$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

KORS MEYER AND PEPPAS RELEASE MODEL

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

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

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

HIXSON-CROWELL RELEASE MODEL

$(100\text{-}Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

IV. Results And Discussion

The present study was aimed to developing gastro retentive floating tablets of Venlaflaxine hydrochloride using various HPMC polymers. All the formulations were evaluated for physicochemical properties and invitro drug release studies.

4.1. ANALYTICAL METHOD

Graphs of Venlaflaxine hydrochloride was taken in Simulated Gastric fluid (pH 1.2) at 225 nm.

TABLE: Observations for graph of Venlaflaxine Hydrochloride in 0.1N HCl (225 nm)

Conc [µg/l]	Abs
5	0.163
10	0.301
15	0.441
20	0.587
25	0.73

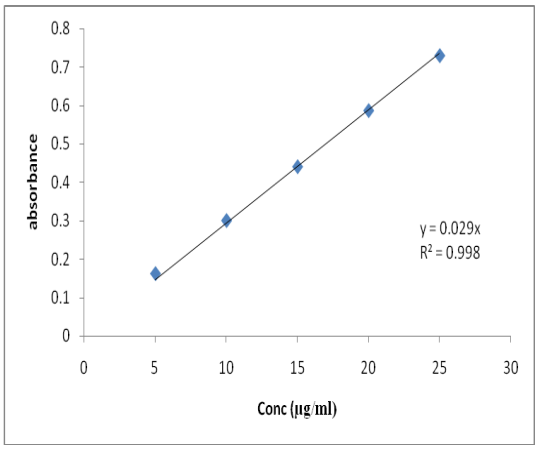

Fig: Standard graph of Venlafaxine hydrochloride in 0.1N HCl

4.2. DRUG – EXCIPIENT COMPATIBILITY STUDIES:
FOURIER TRANSFORM-INFRRED SPECTROSCOPY:

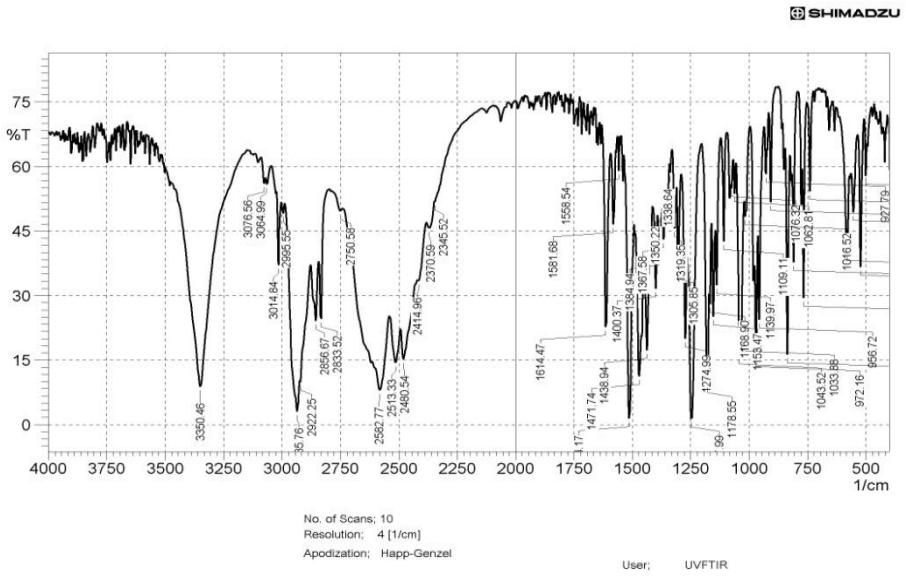

Fig : FT-TR Spectrum of Venlaflaxine Hydrochloride pure drug.

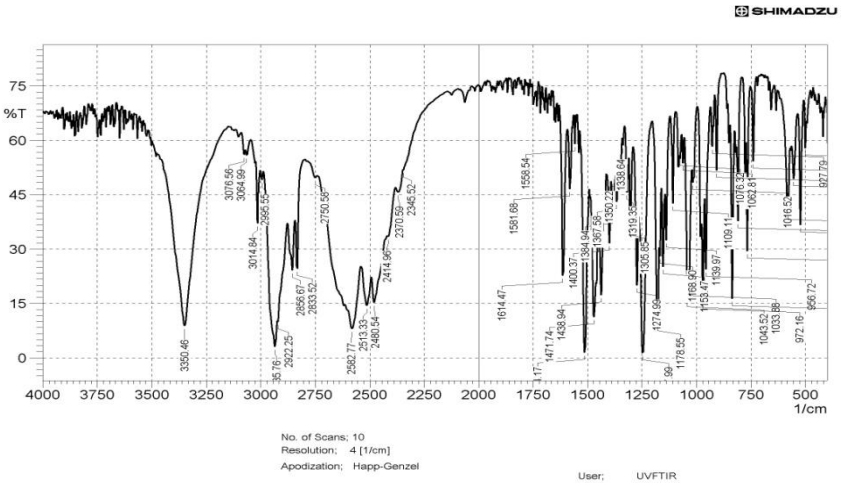

Fig: FT-IR Spectrum of Optimised Formulation

4.3. OPTIMIZATION OF SODIUM BICARBONATE CONCENTRATION :

Three formulations were prepared with varying concentrations of sodium bicarbonate. The formulation containing sodium bicarbonate in 50mg concentration showed less floating lag time of 4 min and the tablet was in floating condition for more than 12 hours.

4.4. IN-VITRO DRUG RELEASE STUDIES:

TABLE: Dissolution Data of Venlaflaxine Hydrochloride Tablets Prepared With Guar gum In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F1	F2	F3	F4
0.5	21.73	18.52	15.36	13.53
1	59.23	37.47	25.93	25.97
2	84.9	59.93	32.75	32.89
3	94.873	65.85	49.65	40.7
4	94.873	77.54	56.34	49.38
5		89.55	64.37	56.2
6		96.6	77.95	67.06
7			86.49	72.52
8			91.65	77.88
9			99.45	86.6
10				89.09
11				94.52
12				99.76

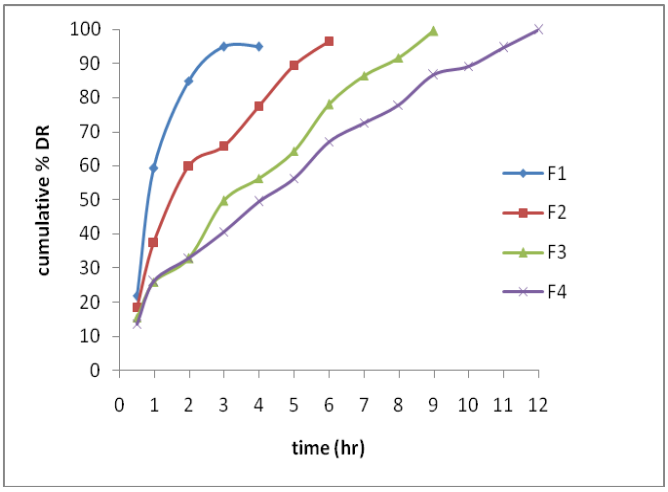

Fig: Dissolution profile of VENLAFLAXINE HCl floating tablets (F1, F2, F3, F4 formulations).

TABLE: Dissolution Data of Venlaflaxine Hydrochloride Tablets Prepared With HPMCK15M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F5	F6	F7	F8
0.5	25.45	23.42	21.43	19.62
1	36.26	39.73	34.35	27.86
2	52.16	47.63	43.27	36.35
3	70.01	54.04	50.35	41.45
4	87.26	62.25	58.92	47.80
5	93.10	71.33	66.45	55.25
6		87.41	72.47	60.24
7		96.84	80.47	66.73
8			89.32	71.34
9			98.54	78.52
10				80.17
11				88.75
12				96.33

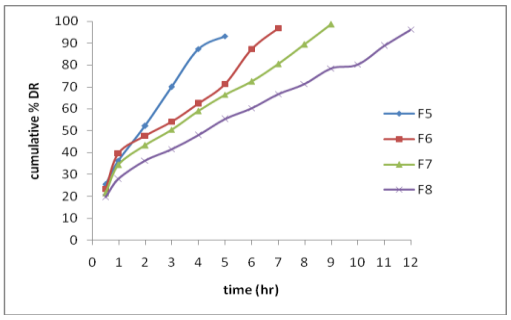

Fig: Dissolution profile of Venlaflaxine HCl floating tablets (F5, F6, F7, F8 formulations).

TABLE: Dissolution Data of Venlaflaxine Hydrochloride Tablets Prepared With HPMC K100M In Different Concentrations

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED			
	F9	F10	F11	F12
0.5	19.81	16.89	13.28	11.21
1	24.02	22.04	18.34	14.87
2	30.70	29.43	25.49	19.19
3	38.32	34.65	30.81	25.66
4	45.25	40.18	35.19	29.32
5	53.28	44.81	41.29	35.06
6	61.92	49.89	47.01	40.13
7	68.08	56.53	54.93	47.63
8	75.44	61.43	59.73	53.71
9	79.22	68.83	64.38	59.34
10	84.90	72.98	70.75	63.27
11	88.83	80.52	74.83	69.86
12	95.90	86.65	80.53	74.97

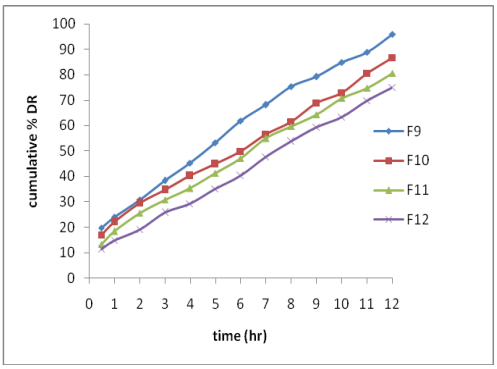

Fig: Dissolution profile of Venlaflaxine HCl floating tablets (F9, F10, F11, F12 formulations)

4.5 APPLICATION OF RELEASE RATE KINETICS TO DISSOLUTION DATA

TABLE: Release kinetics data for optimised formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100
0	0	0			2.000			
13.53	0.5	0.707	1.131	-0.301	1.937	27.060	0.0739	-0.869
25.97	1	1.000	1.414	0.000	1.869	25.970	0.0385	-0.586
32.89	2	1.414	1.517	0.301	1.827	16.445	0.0304	-0.483
40.7	3	1.732	1.610	0.477	1.773	13.567	0.0246	-0.390
49.38	4	2.000	1.694	0.602	1.704	12.345	0.0203	-0.306
56.2	5	2.236	1.750	0.699	1.641	11.240	0.0178	-0.250
67.06	6	2.449	1.826	0.778	1.518	11.177	0.0149	-0.174
72.52	7	2.646	1.860	0.845	1.439	10.360	0.0138	-0.140
77.88	8	2.828	1.891	0.903	1.345	9.735	0.0128	-0.109
86.6	9	3.000	1.938	0.954	1.127	9.622	0.0115	-0.062
89.09	10	3.162	1.950	1.000	1.038	8.909	0.0112	-0.050
94.52	11	3.317	1.976	1.041	0.739	8.593	0.0106	-0.024
99.76	12	3.464	1.999	1.079	-0.620	8.313	0.0100	-0.001

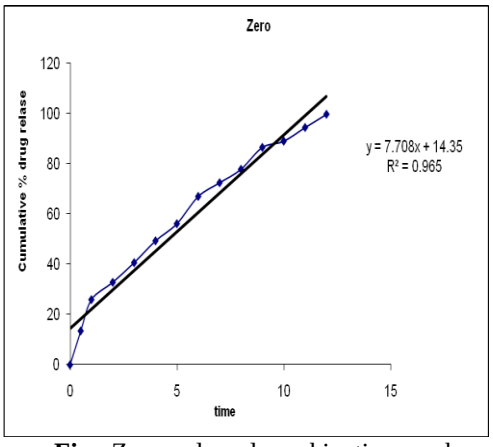

Fig : Zero order release kinetics graph

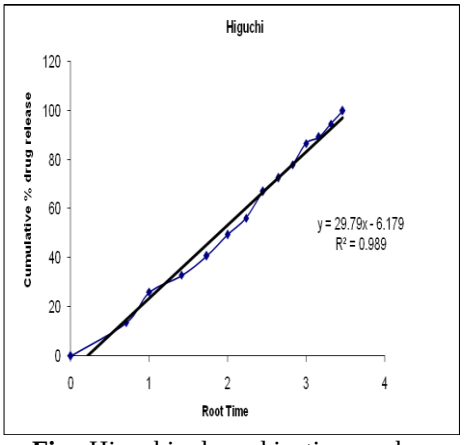

Fig : Higuchi release kinetics graph

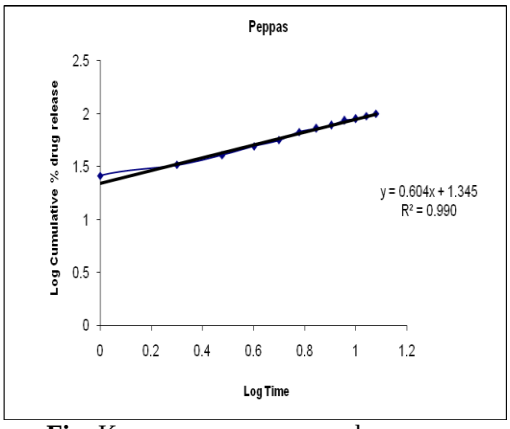

Fig: Kors meyer peppas graph

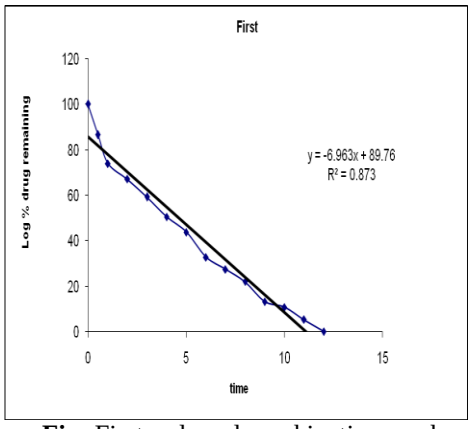

Fig: First order release kinetics graph

From the above graphs it was evident that the formulation F4 was followed non fickian peppas release kinetics.

V. Conclusion

In the present research work the gastro retentive floating matrix formulation of Venlaflaxine hydrochloride by using various hydrophilic polymers. Initially analytical method development was done for the drug molecule. Absorption maxima was determined based on that calibration curve was developed by using different concentrations. Gas generating agent sodium bicarbonate concentration was optimized. Then the formulation was developed by using different concentrations of polymers of various grades of HPMC and Guar gum. The formulation blend was subjected to various preformualation studies, flow properties and all the formulations were found to be good indicating that the powder blend has good flow properties. Among all the formulations the formulations prepared by using Guar gum were in the concentration of 120mg (F4) showed maximum drug release 99.76% in 12 hours with good floating lag time and duration of floating.The formulations prepared with HPMC K 15 M retarded the drug release up to 12 hours in the concentration of 120 mg (F8).The formulations prepared with HPMC K100M were also retarded the drug release for more than 12 hours. Hence they were not considered. The optimized formulation dissolution data was subjected to release kinetics, from the release kinetics data it was evident that the formulation followed peppas mechanism of drug release.

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