Formulation and Development Floating Tablet of Anti Depressant (Venlafaxine Hydrochloride).

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Abstract- The main object in this research study is development, formulation and evaluation of Venlafaxine hydrochloride anti-depressant gastro retentive tablets that is release 24 h time of period in control manner.

Floating drug delivery system use in treatment of depression is the main object on floating drug delivery system mechanism, needs and application and the main focus on used in treatment in depression mental state, floating drug delivery system is extreme valuable process and capability to prolong and control the gastric emptying time which domicile in the stomach for long time and floating system is more significance in enhancement of bioavailability and minimize the drug wastages, depression is most serious mental state today many people is know that depression not disease but it is serious mental disease which is cause anxiety etc. And floating drug delivery system is very useful on those drug which have lower bioavailability and in this disease. And in this mental state patients not want to take medicine two to three times because they not feel good and normal and floating system is most useful for Patients compliance so floating drug delivery system is very applicable in anti-depressant drug for example Venlafaxine hydrochloride.

In this formulation used different type of the apply in this preparation which is HPMC, Carnauba wax, Sodium bi carbonate, cetyl alcohol, Talc, Olive oil as well as drug formulate and give satisfactory and optimal release and stay buoyant on the medium surface the conclusion is obtain success in this formulation and increase in bioavailability as well gastric residence time.

Index Terms- Gastro retentive system, Floating drug delivery system, Depression

I. INTRODUCTION

Oral drug delivery system is aid to arrive to resistance to change of position therapeutic plasma drug concentration in to the preparation. These drug dosage forms disclose good patient compliance and assumption drug release profiles. Moreover these were not constructed to counter the difficulties attached with physiological position of the human body that are gastric emptying which more important effectual the bioavailability and in turn the curative capacity to produce a desired effectual of the drug dosage forms. Thus gastro retentive dosage forms such as hydrodynamic balanced systems, modify density system, GIT release the drug in absorption zone and extended the gastric residence duration by antagonistic gastric emptying method. The groups can controller release of the drug in absorption zone before eviction of the dosage form from the human body thence make proper the bioavailability of the drug.

Gastric emptying of dosage forms is an utmost various method and capability to extended and control emptying time is vital plus for dosage forms, which domicile in the stomach for a large time than conventional dosage forms, while the dosage form is lower absorption/non absorbing phase. These kinds of problems defeat by the floating drug delivery system. It is the gastro retentive drug delivery system.

II. GASTRO-RETENTIVE SYSTEM

Gastro retentive system can stay in the gastric site for many hours and thence importantly extended the gastric retention made better bioavailability minimize drug wastage and make better, solubility of drugs that are less soluble in high pH environment. Gastric retention generate newer curative possibilities and substantial profits from patients.

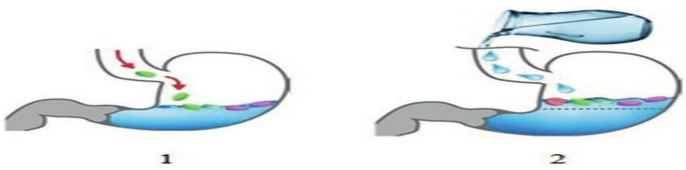
Gastro-retentive system are those dosage form which is able for retain itself in the stomach of gastric content to maximizing the produce absorption drug from medium of acidic in control manner. Gastro retentive system are favourable drug which is improving their.

- Bioavailability
- Therapeutic effective
- Possible reduction
- Reduces drug wastage
- Rise solubility for drug that are less soluble in high pH

III. FLOATING DRUG DELIVERY SYSTEM-

Floating drug delivery system are less density which buoyancy is capable amount for float over the gastric content. It stay buoyant in stomach without affective gastric empty retention time. Conclusion maximize the gastric retention time for better control of fluctuation in plasma drug concentration.

Devis is primarily introduce the floating system that floating drug delivery system to use the difficulty of swelling of dosage form and presented the modern gastro retentive drug delivery system to the pharmaceutical or pharmacy industry. Today the more of effectual control drug release dosage form.



IV. FLOATING DRUG DELIVERY SYSTEM

The main purpose of floating drug delivery system is arrive assuming and maximize in bioavailability. Today pharmaceutical scientist are mostly participate in development of floating drug delivery system. The dosage form has vantage of once dose for cure and should be deliver the active drug material directly at specific site. Floating system is beneficial as drug with narrow absorption window, which is importance for local action to other dosage form of tablets which are absorbed in the stomach. Floating drug delivery system will maximize the bioavailability of the drug from by floating dosage form in the stomach for large duration and produce for extended time and these several kinds of system are significant for narrow absorption. Useful the special category of the dosage form. Gastric emptying is most fast in fasting stage, bulky in the presence of food to slow emptying and give important liquid for efficient buoyancy.

V. TYPE OF THE FLOATING DRUG DELIVERY SYSTEM-

There are two types of the floating drug delivery system-

A)-EFFERVESCENT TYPE OF FLOATING DRUG DELIVERY SYSTEM-

B)-NON EFFERVESCENT TYPE OF FLOATING DRUG DELIVERY SYSTEM-

EFFERVESCENT TYPE- Effervescent type of the floating drug delivery system is also known as the gas generating system which is formulated by the aid of the swelling type polymer such as methyl cellulose, chitosan and several type of effervescent compound like sodium bicarbonate, tartaric acid and citric acid. The relative magnitudes of two quantities of citric acid and sodium bi carbonate is optimal stoichiometric for gas generating in the floating is slightly convexity of the drug delivery system can be neglected by inert gas CO2 by effervescent chemical reaction between organic acid citric acid and carbonate.

MECHANISM OF ACTION- Effervescent system are formulated with aid of the swelling polymers and several types of the effervescent type compounds are apply in formulation when they come in attach with acidic gastric content then they freedom CO2 and gas ensnare in swollen hydro colloids which furnish buoyancy to the dosage form.

NON EFFERVESCENT TYPE- Non effervescent system is made by gel forming largely swell cellulosic hydrocolloids HPMC hydroxyl propyl methyl cellulose, polysaccharides, matrix polymer in large (20%-75%) to tablet capsule, it is non effervescent swelling system. In this technology dosage form is attaches mixing of drug with gel that is swell close interaction with after administration of oral and keep a comparative unity of shape and bulk density of lower than 1.

MECHANISM OF ACTION- After swallowing bang up investment via absorption of a liquid by a solid or gel of gastric fluid to the point which is preclude their outlet from the stomach non effervescent type system is also known as plug type system. First forming a gel at the surface of the dosage form is mechanism of swelling of polymer or bio adhesion to mucosal bed in gastro intestinal tract hydrate by first formed a gel on the surface of drug dosage, conclusion construction of a gel power to determine the diffusion of solvent-in and drug out of the dosage form. Having base on the mechanism on the swelling of polymer or bio-adhesion the mucosal bed in gastro intestinal tract. Resultant diffusion rate of solvent in drug out from dosage form controlled by the gel emphasis.

DEPRESSION

Depression is also known as the Major depressive disorder. The most common and serious medical illness that is negative effectual on feelings, the mode your and how your act, But its treatment is available, depression cause by the emotional state of the feelings of dreary and also lost of interested activities of the joy and happiness. Depression is mainly assortment of emotional and physical difficulties and minimize in ability to process of work at the home and another working place. Feeling down in depression situation- change in brain chemistry cause the depression position. Most scientist or researchers says about depression which is depression is caused by these several factors which is-Hormonal Factors Medical Factors

Depression is the situation of unhappy and sorrow. Today the mostly people suffering from depression because of our modus vivendi is so horrendous. While person are in depression, person provender at every point sad for few days, weeks or months or only some days. Some people think depression is common like normal state and not a real health status but this not correct thought, Depression is real disease with original sign and symptoms. It is not kind of weakness, but treatment is possible and most of person is cure or recover the disease of the depression.
Depression is trivialities status but it is commonly is present in today life. W.H.O World health organization is display the several suffering person how they overcome the depression. And also present the report how many people suffering by this disease 1 in 5 women and 1 in men at same point life duration of time 21% of women and 12% of men are suffering from the depression.

SIGN & SYMPTOMS OF DEPRESSION-

A) Involvement in joy and pleasure is minimize or almost lost.
B) Feeling guiltiness also occur in depression condition cause the weight loss or weight gain in appetite.
C) Problem generate in making decision of thinking or in disease condition.
D) Angriness is over much in depressive mood.
E) Loss of interest in friend family party or get together activities in depression.
F) Biochemistry- Changes of chemical reaction in brain chemistry may be cause of sign and symptom in disease of depression.

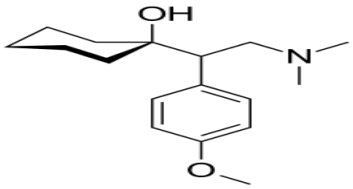
G) Genetics-Depression in hereditary from families 70% of chance cause by the generation.

Venlafaxine. Hydrochloride

- Effexor is the trade name of Venlafaxine HCL of Anti-depressant. It is the antidepressant category of SNRI that is serotonin noradraline reuptake inhibitor.
- SNRI is the maximum the concentration of the neurotransmitter serotonin and noradraline in the brain of the human body.
- It is primarily acquaint by Wyeth in 1993 that is the momentary present in market by the Pfizer.
- It is applied for the therapy of the major depressive Disorder (MDD) that is stature, commonly Anxiety
- Disorder (GAD), Panic disorder and social phobia

VI. DRUG PROFILE

3.1 DRUG DATA - VENLAFAXINE HCL



MOLECULAR STRUCTURE OF THE VENLAFAXINE HYDDROCHLORIDE

Venlafaxine HCL is a serotonin and norepinephrine reuptake inhibitors.

1. Molecular formula: $CH_{27}N_O2HC1$
2. Molecular weight: 313.87
3. Action and use-Inhibition of 5HT and noradranale reuptake; antidepressant:
4. Chemical name: (RS)-1-[2dimethylamino- 1–(4-methoxyphenyl)-ethyl]cyclohexanol.
5. Category: Anti-depressant.
6. Preparation
   i. Prolonged release venlafaxine capsules.
   ii. Prolonged release Venlafaxine Tablets.
   iii. Venlafaxine Tablets.

3.1. Physico-chemical properties:

i. Description: white crystalline powder.
ii. Standards: Venlafaxine HCl contains not less than 98.5 per cent and not greater than of 101.5 percent, measured on the not still wet ground.

Solubility: Venlafaxine HCl is regarded to be soluble in aqueous solutions with pH between 2 and 5. It is sparingly to somewhat soluble in aqueous solution with pH 7.

EXCEPIRNT USED IN FORMULATIONS-

- HPMC
- Cetyl Alcohol
- Talc
- Sodium bi carbonate
- Carnauba wax
- Olive oil

VII. METHODOLOGY

PRE FORMULATION STUDIES

Pre-formulation studies are take put in order to appraise the physical and chemical properties if the drug alone and in the joined form with the receiver.

These research are significant to predict the physical and chemical properties and stability of the drug and additives.

ORGANOLEPTIC PROPERTIES:

1. Color

Take a small amount of sample and trim it on the white paper and analyze it seem.

PHYSICAL PROPERTIES:

1 .Angle of repose

The flow characteristics are determined by angle of repose. Unappropriated flow of powder is due to frictional force are amount by angle of repose Angle of repose is defined as the big angle possible between the surface of a file of the powder and the horizontal plan.

Table No. 1 Flow properties and corresponding Angle of repose

Flow property	Angle of Repose (Degree)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable – may hang up	41-45
Poor –must agitate , vibrate	46-55
Very poor	54-65
Very, very poor	>66

The excellence characteristics of a tablet that prepare it a popular and satisfactory dosage form are denseness, physical stability, fast formation ability, chemical stability and efficacy. In commonly above characteristics of tablet by the quality of the granulation from which it is prepared. Mostly preparation and process liable regard in the granulation step can effectual the characteristics of the granulation generate. Thence many methods to determine certain granulation characteristics have been generated to monitor granulation suitableness for tablet preparation. The chief characteristics required to be proctored in granulation are flow properties and sponginess.

2. Determination of bulk density and tapped density:

A correctly weighed of the powder (W) was had caution poured into the graduated cylinder and the volume (v_0) was measured. Then the graduated cylinder was closed with lid, set into the density measurement setup (bulk density setup) the density setup was set for 500 taps after that, the volume (v_f) was determine and continued operation till the two back to back reading were equilibrium.

The bulk density and taped density was measured by applying the following formulas.

Bulk Density $=W/V_0$

Tapped Density $=W/V_f$

Where, V_0= Initial volume,

V_f = final volume

3. Compressibility index

The compressibility Index and Hauser ratio are determine if the property of a powder to be compressed. Extent they determine the relative significance of inter especial connection. In a free following powder, such connection are commonly lower important, and the bulk and tapped density will be intimate in value. For bad flowing materials, there are often larger inter corpuscle connection, and a larger difference between the bulk tapped density will be obtained. These difference are designated in the compressibility index and the Hausner's ratio.

The compressibility index and hausner's ratio are determined by measuring the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) = $P_{tapped} - P_{bulk}/P_{tapped}$ X100

Hausner ratio = P_{tapped}/P_{bulk}

Chart are following

Table No. 2 Scale of flow ability

Compressibility index (%)	flow character	Hausner Ratio
_< 10	Excellent	1,10-1.11
11-15	Good	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

4 .Melting point:

It is the used for to test the purity of the sample

Procedure:

Take a little amount of sample into the fusion tube. Locate in the tube in the melting point setup contain castor oil maximize the temperature of castor oil bit by bit and write the temperature begin to melt and when all the powder is full done its melts.

5. Solubility:

Take a little amount of sample and mix the solvent until the sample mostly dissolves. It is determined for the presence of any undissolved particles.

6. Drug-excipient compatibility studies:

Drug-excipient compatibility studies are significant to known the connection between drug and excipient and in between excipients of the preparation, which could later effectual the stability of the preparation and may in obstacle with the pharmacological action of the drug.

The physical determination of the preparation is complete while alone and in mixing with the excipients. If there is any change in the physical looks seems that there is connection.

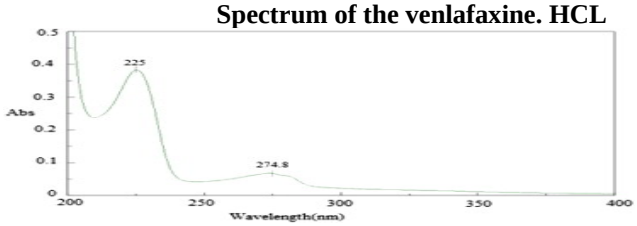
But few substance do not show any physical changes when mixed in a preparation, for such FT-IR (Fourier Transform-infrared) studies are conducted.

Procedure by FT-IR studies:

The FT-IR studies are conducted for Venlafaxine HCL and mixture of Venlafaxine excipients by formulation in potassium bromide discs. The peaks are gained and compare with the standard by bigger imposing these spectra and determined and for any difference in shape and size of spectrum. If there is any importance alteration represents between drug and excipients.

Preparation of the standard curve- Determination of the maximum absorbance

Spectrum of the venlafaxine. HCL



Preparation of 0.1 M Hydrochloric acid:

Correctly determined 8.5 ml of hydrochloric acid and requirement water to make up to 1000 ml.

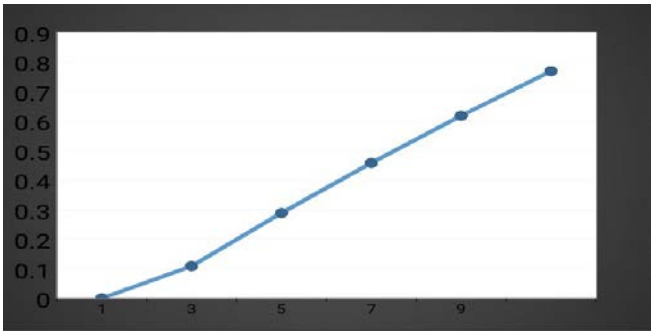
Preparation of stock solution:

Pipette out 10 ml of the above solution and it to a 100 ml volumetric flasks. Then make up the volume to 100 ml with 0.1 M HCL. Then made the standard stock solution withdraw 2ml, 4ml, 6ml, 8ml, and 10ml into five 100 ml different volumetric flasks. Then up the volume to 100 ml with 0.1M HCL to get 2, 4, 6, 8, 10/ml concentration.

CALIBRATION CURVE OF THE VENLAFAXINE HCL:

Concentration in ug /ml	Absorbance in nm
1	0.109
3	0.289
5	0.458
7	0.618
9	0.769

y – 0.088x, r2 - 0.991



Calibration curve of venlafaxine HCL in 0.1 N HCL

CALIBRATION CURVE OF VENLAFAXINE HCL:

The absorbance of the made stock solution was determined at 224 nm in an UV spectrophotometer. Plot a graph between concentration (in ug/ml) vs absorbance (in nm) on \axis and Y-axis respective.

Ingredients	f_1	f_2	f_3	f_4	f_5	f_6	f_7	f_8	f_9	f_{10}	f_{11}	f12
Venlafaxine. Hcl	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
olive oil	80	-	-	120	-	-	160	-	-	200	-	-
Carnauba wax	-	80	-	-	120	-	-	160	-	-	200	-
Cetyl alcohol	-	-	80	-	-	120	-	-	160	-	-	200
H P M C	142	142	142	102	10	102	62	62	62	22	22	22
$NaHCO_3$	50	50	50	50	50	50	50	50	50	50	50	50
Talc	3	3	3	3	3	3	3	3	3	3	3	3

FORMULATION

Steps Involved in Formulation

- Formulate of venlafaxine. Hcl effervescent day thermoplastics granulation
- Effervescent floating tablets. Each and every containing 37.5mg
- Venlafaxine. Hcl were formulated by melt granulation (Hot melt technique). The constituent ingredient of various formulation is presented.
- All the component except was were melted in porcelain dish on hot plate and dosage form was mixed to it.
- Then to this composition another saved component except talc were mixed to it.
- The conclusion mixture was allowed to Solidify at room temperature and then passed by sieved 16 to from granules .the granules were lubricated by mixing talc extra bit by bit.
- The lubricated granules were than compressed into a tablet by applying standard flat – face punches on single punch tableting machine, each and every Tablet containing 37.5mg of venlafaxine. hcl and total tablet weight 312 mg at invariant.

Hot melt Extrusion (Technology)

Hot melt technology is a mostly used in Plastic industry and current time has been presented to be an executable method to formulate many type of dosage forms and drug delivery system. Hot melt technology procedure are recently used in pharmaceutical industry for the manufacture of a many of dosage forms and preparation. HME offers many significance on the old and traditional pharmaceutical methodology or technique the absence of solvents, some processing level, thence low consuming easy and continuous process, large grade of mechanization recognized by regulative authority the capability to method badly compactable material into tablet form and the potentially of the preparation of solid dispersion and better bioavailability.

Principle-

The main object of principle behind HME technology regard adding and melting an active API active pharmaceutical ingredient, pharmaceutical degree polymer and other excipient in a melt extrusion and then forcing it done dies with one or more rotating screw to come into possession the coveted product.

Application-

- Hot melt extrusion can be graduated for the formulation of granules and pellets.
- Hot melt extrusion also applied in formulation of sustained release wax granules.
- Hot melt extrusion showed greater power and better component uniformity.
- Effervescent granules also made by HME show governable rate of effervescence.
- HME has most of uses in formulation of solid dosage forms that is tablet and capsules.

EVALUATION-

. Pre-compression parameters

1. Angele of repose:

Take a little amount of powder (5 gm) in a cone shaped funnel fix it in a holder at a suitable height say 6 cm above the surface. Locate a graph sheet below it. The sample was passed slowly by the funnel. The height of the powder tip was developed. Then determine the perimeter of the heap by construct with the pencil on the graph sheet. The radius of the heap was determined, the angle of repose is measured by application the following formulation. This is repeated five times for correct conclusion.

2. Bulk density and Tapped density:

Weight a little amount of the powder (w) was poured into the graduated cylinder and the volume (v0) was determined. Then, graduated cylinder was closed with lid, set into the density measured setup (Bulk density apparatus) set for 500 taps and change that, the volume (vf) was determined and continued ways till the two back to back readings were equal.

The bulk density and tapped density were measured applying the following preparation.

Bulk Density = W/V0

Tapped Density =W/V_f

Where, V_0 = Initial volume,

Vf = final volume

The conclusion were tabulated.

3. Compressibility index and Hauser ratio:

The compressibility index and Hauser ratio are calculated by determining the values for bulk density (P_{bulk}) and tapped density (P_{tapped}) as follows:

Compressibility -index = P tapped – P bulk /P tapped X 100

Hauser ratio = P tapped / P bulk

The conclusion were tabulated in table

EVALUATION OF FORMULATED TABLES OF VENLAFAXINE HCL

All the prepared sustained release tartlets were evaluated for following official and unofficial parameters.

Weight Variation

Twenty tablets were at random choose from each and individually weighted. The average weight and standard deviation of twenty tablets was measured. The batch passes the test for weight variation test if not more than two of the individual tablets weight deviate from the average weight by more the percentage present in a none aberrant by more than two in one the percentage presented.

Observation:

The average weight and standard deviation of the tablets of each batch were given.

Weight variations-

Derivative - Tablet weight-average weight x 100 / total tablet weight

Table No: 6 Weight variation Specification

Average weight of tablets(X mg)	Percentage deviation
130 or less	±10
130to 324	±7.5
More than 324	±5

1. Dimensions

Control of physical damnation of the tablets is requirement for consumer credence and to maintain tablet to tablet uniformity. The dimensional description were calculated applying digital Vernier calipers. The thickness of tablets is more associate of the tablet hardness can be applied as initial control factors.

Six tablets were especially choose from each batch and their thickness was calculated by using Digital Vernier caliper.

2. Hardness

It is calculated to become best compactness during shipping, coating, and packaging and to get better shape and design. Hardness was calculated by applying hardness tester. (Pfizer hardness tester) for each batch six tablets were tested. The force required to brittle the tablets is noted by the units is kg/cm.

Observation:

The determination hardness of tablets of each batch was range from 6-16kg/cm.

3. Friability

Twenty tablets were weighed and take in the Roche friablater and setup was rotated at 25 rpm for every 4 minutes. After behavior the tablets were weighed again. The percentage friability was determined applying the formula,

%F= {1-(wt/w)} x100

where, %F=friability in percentage

w=initial weight of tablets after revolution

Observation-

All the formulated batches were found in accepted limit of 0.1-0.6 as specified in IP.

4. Buoyancy lag Time

It is measured in order to appraise the time taken by the drug to flat 3on the top of the dissolution medium, after it is located in the medium. These parameters can be calculated as a part of the dissolution test.

The results were tabulated in table.

5-Floating Time

Test for buoyancy is commonly processed in SGF-Simulated Gastric Fluid attached at 37C. The time of duration for which the dosage from currently floats on the dissolution media is termed as floating time.

6-Dissolution study:

Preparation of buffer:

Determine 8.5 ml of HCL in a 1000 ml volumetric flask and make up the volume to 1000 ml applying distilled H20.

Requirements:

Medium 0.1N HCL
Volume: 900 ml
Apparatus: USP II (paddle)
RPM: 50
Time: upto 12 hrs
Temperature: 37 c _+ 0.5oc
max: 224 nm

Process the test in six tablets one tablets in each dissolution vessel containing 900 ml of 0.1 Hcl maintained at 37 c +_ 0.5 c.at specific time of duration removed wanted quantity of sample and replace same quantity of 0.1N Hcl (maintain sink condition), Then obtained was taken and calculator produce.

$$\% \text{ purity} = \frac{\text{absorbance} * 900 * \text{dilution} * 100}{\text{Slope} * 1000 * \text{label claim}}$$

7-Assay:

Break 20 tablets and weight equal to 20 mg Venlafaxine HCL and dissolved on 0.1N HCL and make up volume to 100 ml.

By the separated 10 ml and diluted to 100 ml with 0.1 N HCL. Measure the absorbance at 232 nm in UV spectrophotometer.

1. **Kinetics of drug release**
2. The in -vitro dissolution profile of all batches were attached to Zero order,

First order, Higuchi model and Koresmeyer- Papers model to found the kinetic modeling of drug release. Connection coefficient (r2) values were determined for liner curves conclusion by the fixation analysis of the above plot.

- **Zero-order kinetic model -** Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model –** Cumulative % drug released Vs square root of time.
- **Nordmeyer-Pappas model** – log cumulative % drug released Vs log time.

Zero – order kinetics

Zero order release would be predicted by the following equation:

At = Ao-Kot

A_t - Drug release at time 't'
A_o - Initial drug concentration
K_o - Zero-order rate constant (hr^{-1})

While the data plotted as cumulative % drug release Vs time and the plot is liner, then the data obtain zero-order equal to K_o

Fist order kinetics:

First order release can be predicated by the following equation:

$Log\ C = log\ C_o - K_t/2.303$

C- Amount of drug remained at time (t)
C_o -Initial drug concentration
k- First order rate concentration (hrs-1)

When graph is plotted as log cumulative % remaining Vs time yields a straight line, and then the produce obeys first kinetics. The constant 'K' answering by multiplying 2.303 with the slope values.

Higuchi's Model:

Drug produce from the matrix devices by diffusion has been determined by Following Higuchi's diffusion equation:

Q - Amount of drug release at time (t)
D - Diffusion coefficient of the drug in the matrix
A - Total amount of drug in unit volume of matrix
CS - The solubility of drug in the matrix
ε - Porosity of the matrix
t - Tortuosity
t - Time at which amount of drug released

When the data is poltted as Cumulative % drug released Vs square root of time yields a straight line, indicating that release diffusion mechanisms. The slope is equal to 'K'.

Korsmeyer – Peppas model:

To study the mechanism of drug produce from the microspheres, the in vitro release data were plotted to the well-known exponential equation (Korsmeyer – Pappas model). That is frequently applied to briefly the drug release natured from polymeric systems.

$Mt/Ma = Kt^n$

Mt/Ma – The faction of drug produced of drug at time (t) K-Constant inculpating structural and geometrical characteristics of the drug /polymer system

N-Diffusion exponent to the mechanism of drug produce while the data plotted as log % drug released Vs log time yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y-intercept.

Mechanism of drug release as per Korsmeyer- Peppas equation/peppas model

S.No.	n value	Drug release
1	0 – 0.1	Fickian release
2	0.5 -1.0	Non-Fickian release
3	>1.0	Class II transport

RESULT AND DESCUSSION

Pre formulation Studies:

1 Organoleptic Properties

The tests were performed as per the4 procedure. The results tabulated below.

Test	Specifications/limits	Observations
Colour	White to off-white powder	White to off-white crystalline solid
Odour	Odour less	Odour less

The result complies as per specifications.

Physical properties:

Angle of repose:

It was determined as per procedure. The result were tabulated below.

Table. no. 13. Flow properties

Materials	Angle of repose
Venlafaxine HCl	38.70

The results show that the drug having fair to passable.

Bulk density and tapped density:

It was determined as per procedure. The results were tabulated below.

Table no. 14. Bulk density and tapped density

Material	Bulk density (gm/ml)	Tapped density (gm/ml)
Venlafaxine HCl	0.48	0.59

Powder compressibility: It was determined as per procedure. The results were tabulated below.

Table no. 15. Powder compressibility

Materials	Compressibility index	Hausner's ratio
Venlafaxine HCl	6.84	1.06

Melting point:

It was determined as per procedure. The results were tabulated below.

Table no. 16. Melting point

Material	Melting point range	Result
Venlafaxine HCl	215.217^{0}c	215^{0}c

The result indicates that the Venlafaxine HCl drug was pure one.

Porosity-19%

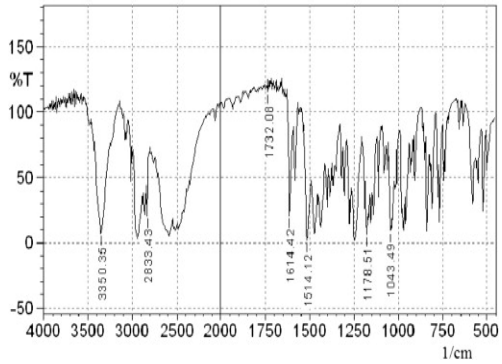
SOLUTION PROPERTIES

Solubility

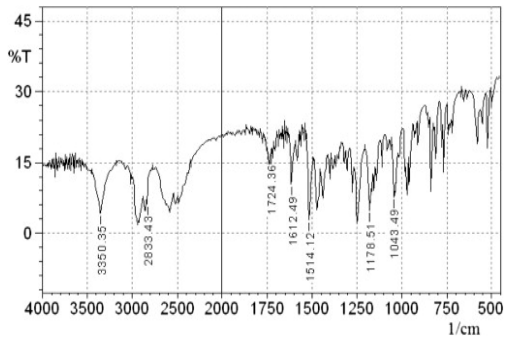
Material	Test	Specification	Observation
Venlafaxine	Solubility	Soluble in water and insoluble inorganic solvent	Complies

Drug-Excipient interaction and identifications

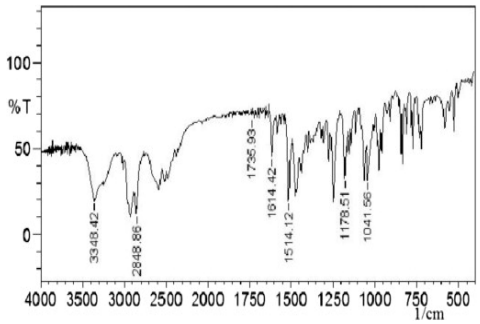
The wavelength of maximum absorbance was obtained at 225.75nm. The calibration cure was found to be linear in the range and straight line equation was obtained having the regression coefficient value of FTIR Spectrum of Venlafaxine HCl showed a characteristic stretching band of o-H at 3350.35 cm-1, aromatic C=H stretching at 1614.42 cm-1, C-O
Stretching at 1514.12 cm-1 and C-N
Stretching at 1178.51 cm^{-1}, C-OC
Stretching at 1043.49 cm^{-1}, C=O
Stretching at 1732.08 cm-1 wave number. These characterstics stretching bands were slightly varied after pre-formulation study, revealing no chemical interaction.



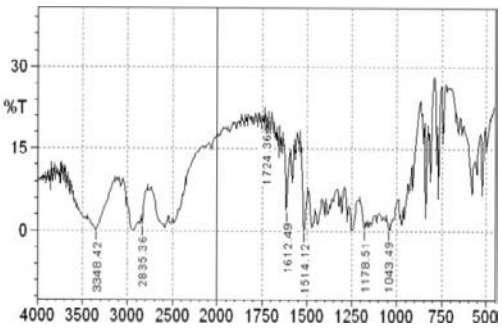
FTIR of the pure drug



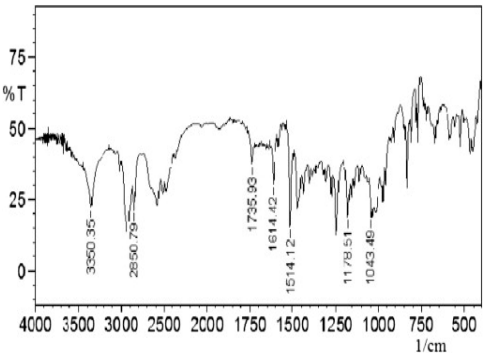
FTIR of the combination of venlafaxine HCL and carnauba wax



FTIR of combination of venlafaxine HCL and Cetyl alcohol



FTIR of combination of venlafaxine HCL and olive oil



FTIR of physical mixture of optimized formulation (F8)

Formulation Development-

The concentration of all the three sleeted hydrophobic retardate (carnauba wax, olive oil and cetylalcohol) was decided on trial basis and error basis. Sodium bicarbonate was incorporated as a gas-generating agent. The trial batches were

conducted to finalize the concentration of sodium bicarbonate. Talc was used as glidant to improve the flow of the granules FTIR study showed that all of retardants/excipients used were compatible with Venlafaxine.

- The use of hydrophilic carrier along with a hydrophilic carrier effectively controls the initial rapid release of a highly water soluble drug such as Venlafaxine. HCl hot melt granulation method (Thermoplastic granulation) is especially more effective in achieving this than the direct compression method.
- Methocel KISM is a good polymer for floating drug delivery system as it is matric forming and low density polymer. Hydrophilic meltable material impart sufficient intergrity to the tablets. Lipids/waxes are considered as an alternative to polymers design of sustained drug delivery system due to their advantages Such as the low melt viscosity (thus avoiding the need of Organic Solvent for Solublization), absence of toxic impurities of drug and also formation of channels with the matrix in the case of a water soluble drug like Venlafaxine HCl. HPMC tablet upon contact with the dissolution medium swell due to the discruption of hydrogen binding among the polymeric chain and from the thick layer of gel eroded over the period of times these parameters are responsible for controlling drug release rate from HPMC tablets.
- **Physical characterstics**-F_1-F_{12} formulation were evaluated for micromeritics showed the pre-compressed blend has a good flow property. Matrix tablet evaluated for physical parameters such as hardness, thickness, weight variation, friability, drug content and swelling index.

EVALUATION PARAMETERS

Formulation code	Angle of Repose	Bulk density (g/ml)	Tapped density (g/ml)
F_1	28.24 ± 0.13	0.408 ± 0.13	0.434 ± 0.11
F_2	27.08 ± 0.02	0.404 ± 0.17	0.439 ± 0.08
F_3	30.11 ± 0.08	0.416 ± 0.05	0.449 ± 0.13
F_4	28.25 ± 0.11	0.408 ± 0.01	0.44 ± 0.03
F_5	28.78 ± 0.14	0.422 ± 0.12	0.464 ± 0.09
F_6	29.54 ± 0.06	0.404 ± 0.04	0.449 ± 0.16
F_7	27.82 ± 0.05	0.415 ± 0.06	0.444 ± 0.11
F_8	27.12 ± 0.18	0.435 ± 0.12	0.478 ± 0.09
F_9	30.78 ± 0.06	0.421 ± 0.05	0.484 ± 0.07
F_{10}	28.45 ± 0.12	0.408 ± 0.05	0.439 ± 0.05
F_{11}	29.65 ± 0.05	0.416 ± 0.14	0.454 ± 0.08
F_{12}	31.24 ± 0.11	0.4123 ± 0.02	0.492 ± 0.12

Formulation code	Compressibility Index (%)	Huascar's Ration	Hardnesss (Kg/cm^3 ± SD)
F_1	5.99 ± 0.04	1.06 ± 0.13	3.10 ± 0.10
F_2	7.97 ± 0.17	1.08 ± 0.08	5.06 ± 0.15
F_3	7.34 ± 0.09	1.07 ± 0.02	2.11 ± 0.12
F_4	8.10 ± 0.08	1.08 ± 0.15	3.46 ± 0.05
F_5	9.05 ± 0.11	1.09 ± 0.06	7.23 ± 0.05
F_6	10.02 ± 0.06	1.11 ± 0.12	2.36 ± 0.11
F_7	6.53 ± 0.15	1.06 ± 0.04	4.38 ± 0.02
F_8	8.99 ± 0.02	1.09 ± 0.11	8.53 ± 0.07
F_9	13.01 ± 0.14	1.14 ± 0.03	2.63 ± 0.05
F_{10}	7.06 ± 0.07	1.07 ± 0.08	3.11 ± 0.07
F_{11}	8.37 ± 0.18	1.09 ± 0.05	7.13 ± 0.11
F_{12}	16.19 ± 0.07	1.19 ± 0.12	2.0 ± 0.10

Formulation code	Thickness (mm ± SD)	Wt. Variation (mg ± SD)	Friability (% w/w)
F_1	3.24 ± 0.055	314.65 ± 2.37	0.58 ± 0.06
F_2	3.33 ± 0.026	314.16 ± 2.06	0.64 ± 10.11
F_3	3.43 ± 0.011	315.55 ± 2.52	0.48 ± 0.02
F_4	3.24 ± .011	315.30 ± 2.26	0.78 ± 0.05
F_5	3.43 ± 0.020	316.00 ± 2.62	0.54 ± 0.02
F_6	3.16 ± 0.015	315.30 ± 2.26	0.67 ± 0.12
F_7	3.55 ± 0.005	316.20 ± 1.89	0.54 ± 0.07

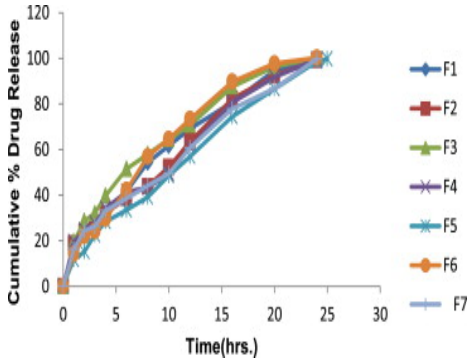
F_8	3.36 ± 0.015	315.33 ± 2.36	0.45 ± 0.11
F_9	3.24 ± 0.015	314.05 ± 1.25	0.64 ± 0.05
F_{10}	3.27 ± 0.05	315.1 ± 2.33	0.72 ± 0.07
F_{11}	3.58 ± 0.010	313.9 ± 1.66	0.59 ± 0.13
F_{12}	3.26 ± 0.20	314.4 ± 2.06	0.68 ± 0.02

Formulation code	**Drug content (% ± 0.14**	**FLT (Sec ± SD)**	**FD (h)**	**SI (% ± SD)**
F_1	99.2 ± 0.14	28 ± 2.2	<24	91.36 ± 6.34
F_2	98.6 ± 0.12	24 ± 2.8	<24	88.8 ± 0.28
F_3	100.5 ± 0.09	26 ± 3.1	<24	90.4 ± 0.38
F_4	98.6 ± 0.05	32 ± 2.4	<24	80.8 ± 0.4
F_5	99.8 ± 0.12	28 ± 2.5	<24	83.04 ± 0.26
F_6	98.5 ± 0.02	38 ± 3.2	<24	81.44 ± 0.33
F_7	97.8 ± 0.05	62 ± 2.7	<24	44.16 ± 0.33
F_8	101.2 ± 0.15	55 ± 2.5	<24	53.92 ± 0.38
F_9	99.4 ± 0.08	69 ± 2.8	<24	47.52 ± 0.42
F_{10}	97.3 ± 0.15	98 ± 3.2	<24	31.8 ± 0.25
F_{11}	102.1 ± 0.08	72 ± 3.4	<24	30.56 ± 0.42
F_{12}	99.3 ± 0.12	104 ± 3.1	<24	34.4 ± 0.28

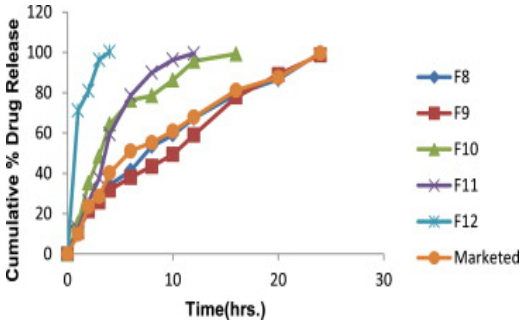
Evaluation of buoyancy of the tablets-

In vitro buoyancy variations for all the formation sodium bicarbonate used effervescent base which generates carbon dioxide gas in the presence of hydrochloric acid present in medicine. The gas generated is trapped and protected with in gel formed by HPMC), thus decrease the density of the tablets. As falls density of tablet below 1 (density of water), tablet become buoyant. $NaHCO_3$ song produced tablets with lag time less than a minute in formulations F_1-F_6 and F_8 more than one but less than 2 minute in formulation F_1 and F_1-F_{12}. It was found that the tablets of formulations F_1, F_2, F_4, F_5 and F_1-F_9 floated buffer for duration more than 24 hours and tablets of formulation F_3, F_6 and F_{10}-F_{12} floated in the buffer solutions for less than 24 hours. The formulation containing carnuba was showed superiority in floating duration as well as maintained the integrity of formulation due to more hardness to others.

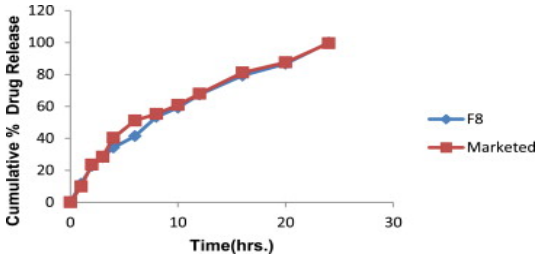
In-Vitro drug release-



In vitro drug release profiles of formulation F1 to F7



In vitro drug release profile of the formulations F8 to F12 and marketed



In vitro drug release profile of optimized and marketed formulation

In-vitro studies performed in 0.1 N HCl (1.2 pH) and result depicted. Formulation F_7, F_8 and F_9 showed release for 24 hours upto 99.62, 99.9 and 98.75% respectively. Marketed tablets showed 99.54% release in 24 hours. Formulation F_1, F_2, F_3, F_4 and F_6 showed release less than 24 h, F_1 F_2, and F_3 each had hydrophilic retardant in concentration 80 mg which is less sustained effect while formulation F_5 showed more than 24 h as an incipient because even of concentration was 120 mg (lesser). The Sustained effect was more due to combination of hydrophilic polymer and hydrophilic retardants (carnauba was) showed good effect in less concentration. Hydrophilic polymer was used as sustaining agent, gas (carbon-di-oxide) entrapping agent and also as filter entrapping and also as filter.

Formulation F10, F1 and F12 failed to show sustained effect may be due to less concentration of hydrophilic polymer and thus unable to form good matrix. All the three retardants in concentration of 160mg. In formulation F7, F8 and F9 showed desired release for 24 h but after comparing with marketed formulation (ventab-XL) (37.5mg). It was similar to it and hence formulations F8 was considered as optimized formulation. The similarity and dissimilarity factor comparison is showed on the table similarity and dissimilarity factor. Independent t-test also proved that F8 was the best formulation as the maximum time points of F8 and F> 0.05 (.e. retaining the Null's hypothesis) compared to other formulation proving that is most similar to marketed product. The amount of hydrophilic retardant was found to be inversely proportional to rate of release. Cetyl alcohol showed good results. Olive oil showed better and carnauba was showed best result.

Formulation	**F1 Value**	**F2 Value**
F_1	9	62
F_2	14	56
F_3	8	64
F_4	15	54
F_5	20	47
F_6	13	57
F_7	14	54
F_8	6	68
F_9	14	54
F_{10}	39	34
F_{11}	37	31
F_{12}	62	21

Table show similarity and dissimilarity factor comparison is showed the F8 regarding as the optimized formulation

Time points	**t-statistic**	**df**	**Two-tailed probability (p)**
1	4.53	10	10 00011
2	2.03	10	10 0.0693

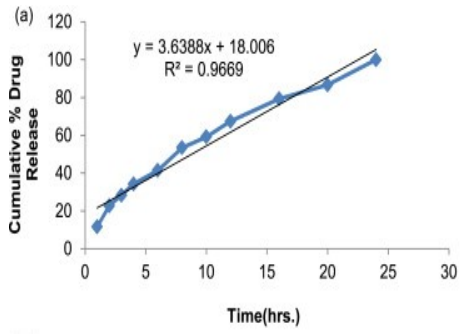
3	0.46	10	10 0.6551
4	16.84	10	10 0.0000
6	16.92	10	10 0.0000
8	5.47	10	10 0.0003
10	3.62	10	10 0.0046
12	5.707	10	10 0.1187
16	5.559	10	10 0.0002
20	1.755	10	10 0.1098
24	1.112	10	10 0.2923

Independent t-test Values for comparison between F8 and marketed product.

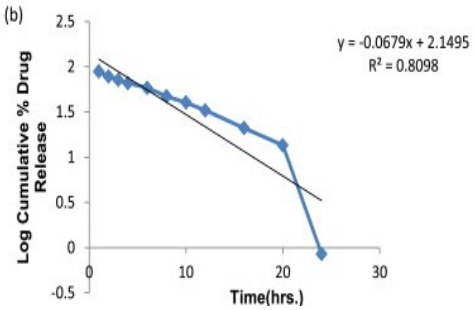
Hardness also played an important role in release. Formulations F_8 had the higher hardness value and hence showed good sustained property. Formulation made with cetyl alcohol i.e. F_3, F_6, F_9 and F_{12} had least hardness and thus had less sustained effect compared to other formulations. But as an exception F_9 showed release upto 24 hours thus it can be concluded that cetyl alcohol also shows good release in the concentration 160 mg. Hardens obtained with the tablets of carnauba was higher where as with olive oil it was moderate and cetyl alcohol tablets showed least hardness.

Stability Studies- According to ICH guidelines, three months stability studies conducted at controlled temperature 40^0C $\pm$ 2^0C and humidity 75 $\pm$ 5% RH .

Showed negligible	**Changes**	**In results**
Parameters	After 30 days	After 60 days
Physical appearance	No Change	No Change
Weight variation (mg $\pm$ SD)	315.33 $\pm$ 2.26	315.28 $\pm$ 2.1
Thickness (mm $\pm$ SD)	3.36 $\pm$ 0.015	3.38 $\pm$ 0.021
Hardness (Kg (Cm^2 $\pm$ SD)	8.53 $\pm$ 0.07	8.53 $\pm$ 0.11
Friability (%$\pm$ SD)	0.45 $\pm$ 0.11	0.45 $\pm$ 0.08
Drug content (%)	101.2 $\pm$ 0.15	101.12 $\pm$ 0.32
Buayancy lagtime (Sec $\pm$ SD)	55 $\pm$ 2.5	56 $\pm$ 2.9
Duration of floating (h)	>24	>24



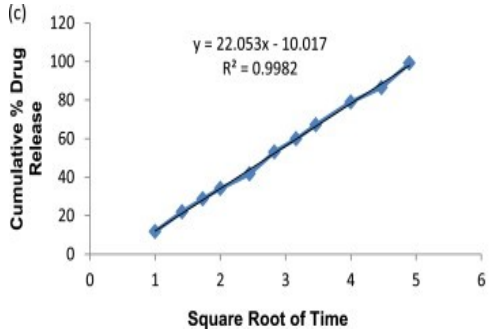
Zero order plot



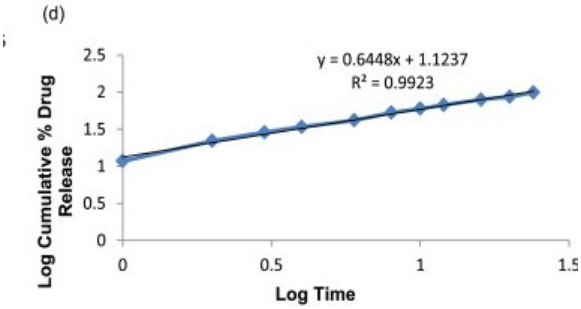
First order plot

Kinetic analysis of release data-

Kinetic evaluation of the optimized formulation of optimized formulation



Higuchi plot



Korsmeyer- Peppas plot

To understand the rate and mechanisms of drug release from optimized tablet formations, dissolution data was fitted into different release Kinetic model The model that best fitted the release data was selected based on the correlation coefficient value (rz) obtained from various Kinetic model. In vitro drug release profile from all these formulations could be best expressed by Korsmeyer Peppas Equation and higuchi Equations as plot showed highest linearity with R2 value 0.9164-0.9961 and 0.9805-0.9982 respectively. In Korsmeyer-Peppas Equation, linear plot was for optimized formulation with high correlation coefficient (r2) value 0.9923 and higuchi value 8.9982. Also, Korsmeyer-Peppas Equation's 'n' values for all formulations except F12 were above 0.5. It was concluded that the optimized formulation followed mixed mechanism of diffusion and erosion, so called anomalous/Non-Fickian diffusion mechanism for drug release.

Formulation	**Zero Order**	**First Order**	**Higuchi**	**Korsmeyer Peppas**		**Release mechanism**
	R2	R2	R2	R2	N	Non Fickion
F_1	0.9827	0.8366	0.9922	0.9902	0.614	Non-Fickian
F_2	0.9923	0.8344	0.97	0.973	0.5624	Non-Fickian
F_3	0.9748	0.9272	0.9968	0.9961	0.5395	Non-Fickian
F_4	0.991	0.7314	0.9595	0.966	0.544	Non-Fickian
F_5	0.9925	0.7918	0.9805	0.992	0.6961	Non-Fickian
F_6	0.9671	0.9025	0.9851	0.992	0.6685	Non-Fickian
F_7	0.9924	0.7335	0.9736	0.9778	0.5651	Non-Fickian
F_8	0.9669	0.8098	0.9982	0.9809	0.5651	Non-Fickian
F_9	0.9878	0.8434	0.9822	0.9923	0.6448	Non-Fickian
F_{10}	0.8293	0.9215	0.9352	0.9848	0.6711	Non-Fickian
F_{11}	0.9031	0.9474	0.9652	0.9164	0.63	Non-Fickian
F_{12}	0.9573	0.8908	0.9659	0.9638	0.849	Non-Fickian

VIII. CONCLUSION

The effervescent-based floating drug delivery system was the promising system. The use of hydrophilic retardant and hydrophilic polymer in combination had its own advantages of maintaining integrity and buoyancy of tablets and also initial burst effect was minimized. It could be concluded that for proper floating duration and in-vitro release the hydrophilic retardant and hydrophilic polymer must be used in polymer must be used in polymer must be used in proper ration, formulation F8 Showed release similar to marketed tablet and was considered optimized formulation. F8 followed zero order, Higuchi and Korsmeyer-Peppas release Kinetics-Peppas release Kinetics. The aim of preparation of Gastro retentive tablets of Venlafaxine HCl was achieved

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