Research Article

Development and Characterization of Gastroretentive Floating Tablets of Venlafaxine Hydrochloride by Thermoplastic Granulation Technique

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ABSTRACT

Gastro retentive dosage forms (GRDFs) is the most feasible approach for achieving a prolonged and predictable drug delivery profile in the gastrointestinal tract. They control the gastric residence time of the drug. The aim of the present study is to formulate, develop and characterize gastroretentive floating tablet of an antidepressant drug Venlafaxine HCl. Venlafaxine HCl is a BCS class I drug having high solubility and permeability. The main objective of the study was to retain the drug in the gastric environment to prolong the drug release time. Twelve formulations were prepared by varying ratios of hydrophobic retardants such as carnauba wax, white paraffin wax, compritol ATO 888 and cetyl alcohol in combination with hydrophilic polymer HPMC K15M. The FTIR and DSC indicated compatibility between the drug and polymers used. The tablets were prepared by hot melt or Thermoplastic granulation method and were evaluated for various parameters such as tablet hardness, weight variation, friability, floating time and *in vitro* drug release profile. Formulation S6 with hydrophobic polymer cetyl alcohol and hydrophilic polymer HPMC K15M in the ratio of 1:3 was the optimized formulation. The optimized formulation showed sustained release of drug for a period of 12 h.

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INTRODUCTION:

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [1]. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time i.e. Gastro Retentive Dosage Forms (GRDFs). These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in absorption of drug for the intended duration of time. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs. Thus, control of release of a drug in a specific region of the GI tract offers numerous advantages, especially for drug exhibiting an 'absorption window' in the GI tract. The intimate contact of the drug with the absorbing membrane and also the potential to maximize drug absorption may influence the rate of drug absorption [2].

Over the last two decades, number of GRDDS has been designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery [3].

Melt granulation (also defined as thermoplastic granulation) operates via similar principles as wet granulation. In this technique, the binder solution of the standard wet granulation process is replaced with a meltable binder such as a wax or polyethylene glycol (PEG), which is either added in solid form, or melted during the process by adding the necessary energy or in the form of molten liquid, optionally containing the dispersed drug [4].

Following particle agglomeration and consolidation, the granules are cooled to room temperature and the solidified binder forms bridges between individual powder particles to yield a solid end product with a granular structure [5].

MATERIALS AND METHODS:

Materials:

Venlafaxine HCl, HPMC K15M were obtained from Yarrow chem products, Mumbai. Sodium bicarbonate was purchased from Finar chemicals limited, Ahmedabad. White Paraffin Wax from Merck Specialities Private Limited, Mumbai and Cetyl alcohol from Sisco research laboratories, Mumbai. Carnauba wax, Compritol® ATO and talc were obtained from Otto Chemika Biochemika reagents.

Method:

Effervescent floating tablets, each containing 75 mg of Venlafaxine HCl were prepared by thermoplastic granulation method [6]. Each floating tablet was prepared by employing sodium bicarbonate as a gas generating agent and water soluble polymer HPMC K15M as hydrophilic matrix. In order to get longer duration of time and to retain the dosage form in the stomach for a long period of time and avoid gastric emptying, hydrophobic polymers (carnauba wax, white paraffin wax, cetyl alcohol, compritol 888 ATP) were also included. All these ingredients except wax were passed through sieve 40. The wax/oil was melted in porcelain dish or beaker on hot plate and drug was added to it. Then to this mixture other sieved ingredients except talc were added. The resultant mixture was allowed to solidify at room temperature and then passed through sieve 20 to form granules. The granules were lubricated by adding talc extra granularly. The lubricated granules were then compressed into a tablet using 10 mm standard flat face punches on a multi punch tablet machine (Karnavati make). Each tablet contains 75 mg of Venlafaxine HCl and total tablet weight was kept constant at 300 mg.

The intention of adhering the dosage form to the inner wall of the stomach is to control the release of drug from the dosage form.

Table 1: Formulation of venlafaxine HCl Floating tablets (Batch size 50)

Ingredients (mg/tab)	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
Venlafaxine HCl	75	75	75	75	75	75	75	75	75	75	75	75
Carnauba wax	85	127.5	42.5	-	-	-	-	-	-	-	-	-
Cetyl alcohol	-	-	-	85	127.5	42.5	-	-	-	-	-	-
White paraffin wax	-	-	-	-	-	-	85	127.5	42.5	-	-	-
Compritol 888	-	-	-	-	-	-	-	-	-	85	127.5	42.5
HPMC K15M	85	42.5	127.5	85	42.5	127.5	85	42.5	127.5	85	42.5	127.5
Sodium bi carbonate	50	50	50	50	50	50	50	50	50	50	50	50
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total weight	300	300	300	300	300	300	300	300	300	300	300	300

EVALUATION PARAMETERS:

Drug-Excipient Compatibility Studies:

In order to identify any physicochemical interaction between drug and excipients, drug venlafaxine HCl and excipients were taken in different ratios, triturated and kept in glass vials for six months, samples were physically verified. There was no clump formation or discoloration of the powdered mixtures inside the vials. This indicated that there was no significant interaction occurred between drug and excipients during storage. So, it was confirmed that drug and excipients were compatible with each other [7]. Furthermore, compatibility studies were performed for the drug and physical mixtures of the drug and excipients by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC).

Pre compression parameters: The powdered blend was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

Post compression parameters:

Tablets were evaluated for its various parameters such as thickness, diameter, hardness, content uniformity, friability, and uniformity of weight. Other specific evolution tests for GRDDS like floating lag time and total floating time and release rate of drug were also evaluated [8].

Diameter: Thickness and diameter of tablets were important for uniformity of tablet size and were measured using vernier calipers.

Hardness: Hardness is a force required to break a tablet across the diameter. Hardness was measured with Monsanto hardness tester in terms of (kg/cm^2).

Thickness: The thickness of the tablets was measured by screw gauge or vernier calipers. It is expressed in mm.

Friability: The percent loss in weight or friability (f) was calculated by the formula given below using Roche fribilator.

$$F = (1-W/W_0) \times 100$$

Uniformity of weight: The test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range.

Table2: USP standards for uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	130 mg or less	±10
2	130 mg to 324mg	±7.5
3	More than 324mg	±5

Content uniformity:

This test is performed to maintain the uniformity of drug content in each tablet which should be in the prescribed range according to the Indian pharmacopoeia 2016. The content uniformity test is mandatory for tablets whose average weight is below 50 mg.

***In vitro* buoyancy determination:**

The *in-vitro* buoyancy was characterized by floating lag time and total floating time. The time required for the formulation to rise to the surface of the dissolution medium was noted as floating lag time and the time for which the tablet constantly floats on the surface of the medium (duration of floating), was measured [9].

Fig.1 *In vitro* buoyancy of Venlafaxine HCl floating tablets

***In vitro* dissolution studies:**

The release rate of Venlafaxine HCl floating tablets was determined using USP type II apparatus, Electrolab. The dissolution test was performed, using 900 ml of 0.1 N HCl, at 37 ± 0.5 °C at 50 rpm for 12 h. A 5 ml sample was withdrawn from the dissolution apparatus at specified time and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 mm Whatman filter papernd sufficiently diluted. Absorbance of these solutions was measured at 225 nm using Agilent UV-visible spectrophotometer.

Fig.2: *In vitro* dissolution of venlafaxine HCl floating tablets

Swelling index: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulations was studied [10].

$$\textbf{\% Swelling Index (SI)} = \frac{W2-W1}{W1} \times 100$$

FTIR: The FT-IR spectra of pure drug, polymers and optimized formulation were scanned over a frequency range 4000-400 cm^{-1} by placing sample on diamond ATR and analyzing for the presence of characteristic peaks.

DSC:

DSC was performed using DSC calorimeter to study the thermal behavior of pure drug, polymers and mixture of optimized formulation. The required amounts of samples were heated in sealed aluminium pans under nitrogen flow (30ml/min) at a scanning rate 5°C per min from 40 °C to 250 °C. The heat flow as a function of temperature and enthalpy change was measured for the drug, polymers and mixture of optimized formulation.

Kinetic analysis of dissolution data: The release profile of venlafaxine HCl for different formulations were fitted to different kinetic model such as Zero order, First order, Higuchi, Korsmeyer/ Peppas to find the release pattern of drug from the formulations.

Zero order kinetics:

Zero order release would be predicted by the following equation

$$A_t = A_0 - K_0 t$$

When the data is plotted as cumulative % drug release versus time, if the plot is linear than the data obeys Zero– order release kinetic, with a slope equal to K_o.

First order kinetics:

First-order release would be predicted by the following equation:

$$\log C = \log C_0 - K_t / 2.303$$

When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant K can be obtained by multiplying 2.303 with slope values.

Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\ \varepsilon/\tau\ (2A-\varepsilon C_s)\ C_s\ t]^{½}$$

Above equation may be simplified if one assumes that 'D', 'C_s' and 'A' are constant. Then equation becomes $Q= Ktl^{1/2}$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, that the drug was released by diffusion mechanism. The slope is equal to **'K'**.

Korsmeyer equation/ Peppa's model:

To study the mechanism of drug release from the sustained release floating tablets of venlafaxine HCl, the release data were also fitted to the well-known exponential equation (Korsmeyer equation/ peppa's law equation), which is often used to describe the drug release behaviour from polymeric systems [11].

$$M_t/M_a = K^n t$$

Table 3: Mechanism of drug release as per Korsmeyer equation/ Peppas's Model

S. No	N value	Drug release
1	>0.45	Fickian release
2	0.45 <n <0.89	Non-Fickian release
3	N<0.89	Case II transport

RESULTS:

Characterization of Active Pharmaceutical Ingredient (API):

UV spectroscopy for determination of λ_{max}:

UV scanning for standard solution of venlafaxine HCl is diluted with 1.2 pH of

0.1N HCl the wavelength of maximum absorption was found to be at 225 nm that is similar to the values given in literature review.

Melting point:

The melting point determination of the drug sample was carried out by melting point apparatus as well as DSC and found to be 216°C. [12].

Drug-Polymer Compatibility study by FTIR

Drug polymer interaction can be studied by FTIR analysis. The FTIR spectrum of Venlafaxine HCl showed a characteristic stretching band of O-H at 3349.0 cm^{-1}, aromatic C=H stretching at 1613.3 cm^{-1}, C-O stretching at 1513.3 cm^{-1} and C-N stretching at 1177.8 cm^{-1}, C-O-C stretching at 1772.3 cm^{-1} wave number. These characteristic stretching bands were slightly varied after pre-formulation study, revealing no chemical interaction.

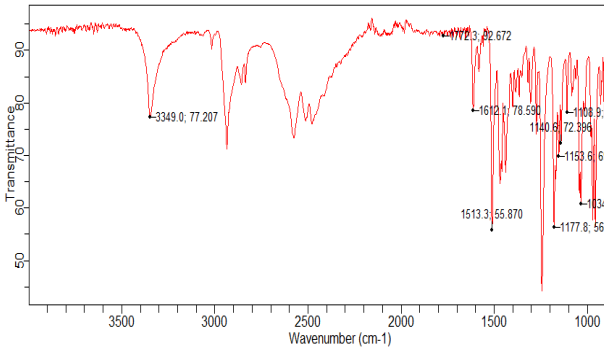

Fig.3: FTIR spectra of pure drug venlafaxine HCl

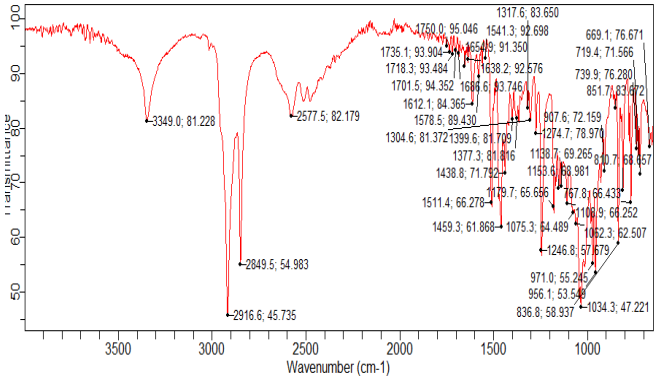

Fig.4: FTIR Spectra of Optimized formulation

DSC:

From the DSC analysis of pure drug and formulation it was observed that there was no significant interaction between the drug and polymers used in the formulation of floating tablets. The DSC thermo gram showed a sharp endothermic peak at 212.21 °C which is corresponding to melting point of the drug. Pre-formulation study indicated the slight broadening and shifting of endothermic peak due to melting effect of hydrophilic polymers and hydrophobic retardants [13].

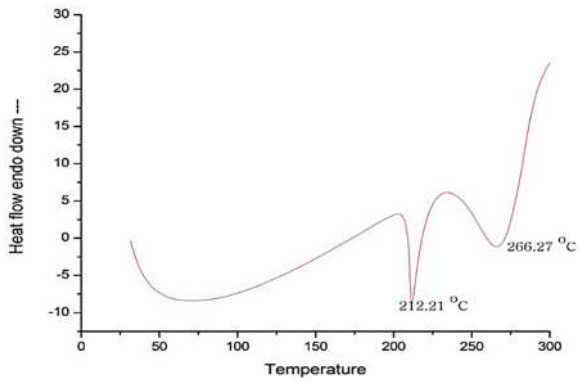

Fig.5: DSC curve of pure drug Venlafaxine HCl

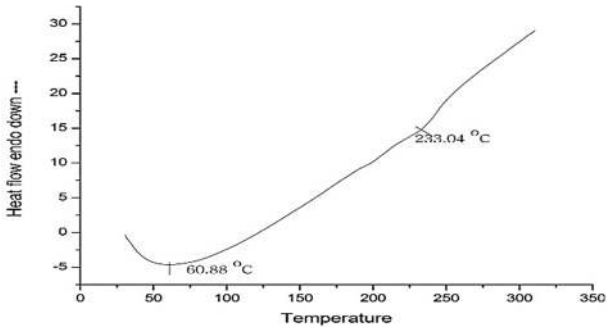

Fig.6: DSC curve of optimised Formulation

Micromeritic studies:

Flow properties of Venlafaxine HCl:

Table 5: Micromeritic property evaluation of drug

S. No	Properties	Values
01	Loose bulk density(LBD) (g/cm^3)	0.352
02	Tapped bulk density(TBD) (g/cm^3)	0.512
03	Angle of repose = $\tan^{-1}(h/r)$	33°
04	Carr's index (%)	31.35
05	Hausner's ratio	1.45

The results of micromeritic properties are presented in table 5. Pure/plain venlafaxine HCl exhibited angle of repose value 33° indicating that the drug contains good flow property. It was further supported by high Carr's index value. Hence it was necessary to use suitable filler like microcrystalline cellulose. The incorporation of these fillers into pure drugs improved the flow properties as indicated by reduction in the values of angle of repose and Carr's index [14].

Pre-Compression Evaluation:

Flow properties of Venlafaxine HCl along with excipients (S1-S12):

The granules of all the formulations (S1-S12) were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio showed the pre-compressed blend has good flow property. [15]

It was found that all the granules have good flow property as they showed angle of repose value between 25-30°, represents good flow property. Carr's index value was found to be less than 10 showing excellent property as they showed Carr's index value between 8.75-19.02. Hausner's ratio was found to be less than 1.12 showing excellent flow property as they showed the value between 1.0012-1.2355.

Table 6: Micromeretic properties parameters of different formulations of Venalafaxine HCl

Formulation	Angle of repose θ	Loose bulk density (g/ml)	Tapped bulk density	Carr's index (%)	Hausner's ratio
S1	27.1±0.08	0.312±0.01	0.364±0.02	14.28±1.4	1.16±0.02
S2	26.46±0.55	0.361±0.03	0.424±0.03	14.85±0.9	1.17±0.01
S3	24.89±2.12	0.329±0.002	0.381±0.007	13.64±2.11	1.15±0.035
S4	25.67±1.34	0.343±0.01	0.412±0.02	16.74±0.99	1.20±0.015
S5	27.47±0.45	0.325±0.002	0.394±0.005	17.51±1.76	1.21±0.02
S6	24.77±2.24	0.319±0.008	0.350±0.03	18.75±0.72	1.09±0.09
S7	28.21±1.19	0.311±0.01	0.391±0.002	20.46±4.71	1.25±0.06
S8	25.89±1.12	0.328±0.001	0.378±0.01	13.22±2.53	1.15±0.035
S9	30.86±3.84	0.3451±0.01	0.4161±0.02	17.06±1.31	1.20±0.01
S10	32.19±5.17	0.370±0.04	0.4228±0.03	12.48±3.27	1.14±0.04
S11	27.64±0.62	0.318±0.009	0.407±0.01	21.86±6.11	1.27±0.085
S12	24.86±2.15	0.362±0.03	0.421±0.03	14.71±1.04	1.16±0.025

Post Compression Studies:

The compressed tablets were evaluated for various post compression parameters such as Uniformity of weight, hardness, friability, content uniformity and *in vitro* dissolution studies to study the quality control of the prepared batches of tablets.

Table 7: Post Compression evaluation of different formulations of venalafaxine HCl

Formulation	Uniformity of weight (mg)	Hardness Kg/cm^2	Friability (%)	Drug content (%)
S1	300±0.63	8.5±1.2	0.333±0.17	95.21±0.8
S2	299±0.38	7.2±0.1	0.334±0.17	97.36±1.35
S3	301±1.62	8.3±1	0.332±0.17	96.23±0.22
S4	303±3.62	7.0±0.3	0.331±0.17	98.21±2.20
S5	298±1.38	7.5±0.2	0.671±0.17	95.34±0.67
S6	300±0.63	8.5±1.2	0.333±0.17	99.56±3.55
S7	295±4.38	7.0±0.3	0.677±0.18	96.23±0.22
S8	301±1.62	6.5±0.8	0.664±0.16	97.81±1.80
S9	300±0.63	6.0±1.3	0.666±0.17	97.25±1.24
S10	298±1.38	6.8±0.5	0.671±0.17	99.12±3.11
S11	296±3.38	7.0±0.3	0.337±0.16	97.51±1.50
S12	301±1.62	6.5±0.8	0.996±0.50	96.23±0.22

All values are mean± standard deviation n=3;

Table 8: *In vitro* buoyancy studies of venlafaxine HCl

Formulation code	F.L.T (Sec) {buoyancy time}	T.F.T (hrs)	Swelling Index (%)
S1	54	>16	78.92
S2	43	>17	77.74
S3	34	>18	88.25
S4	43	<15	84.40
S5	54	<16	87.95
S6	39	>16	90.33
S7	28	<16	66.24
S8	44	>18	60.61
S9	20	>18	59.23
S10	30	<16	64.51
S11	13	>16	62.01
S12	16	>18	56.33

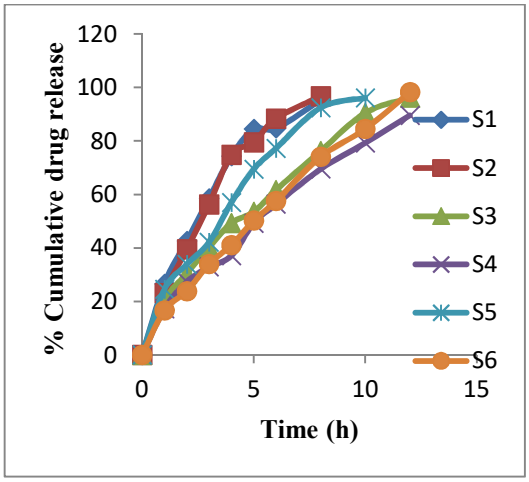

Fig.7: Dissolution profile of formulations (S1-S6)

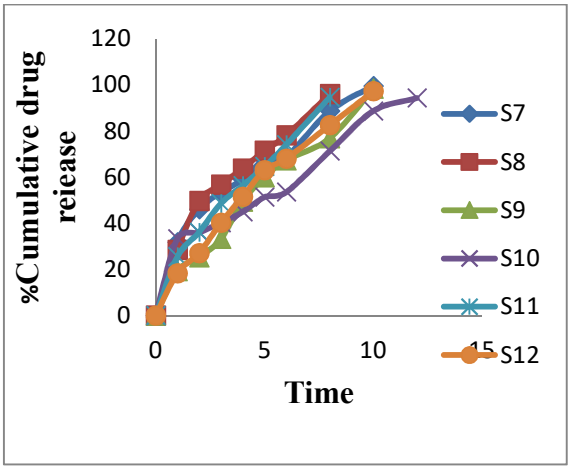

Fig. 8: Dissolution profile of formulations (S7-S12)

Table 9: Correlation coefficient values of S1 to S12 formulations.

Formulation	Zero order	First order	Higuchi	Koresmayer/ Peppas	
	R^2	R^2	R^2	R^2	n
S1	0.948	0.859	0.957	0.966	0.600
S2	0.919	0.816	0.974	0.977	0.719
S3	0.984	0.891	0.992	0.997	0.639
S4	0.988	0.907	0.985	0.989	0.673
S5	0.953	0.881	0.978	0.981	0.646
S6	**0.993**	**0.824**	**0.989**	**0.995**	**0.741**
S7	0.982	0.919	0.981	0.985	0.478
S8	0.965	0.862	0.984	0.978	0.545
S9	0.981	0.910	0.973	0.973	0.744
S10	0.977	0.986	0.921	0.887	0.447
S11	0.988	0.917	0.988	0.994	0.625
S12	0.982	0.879	0.993	0.993	0.741

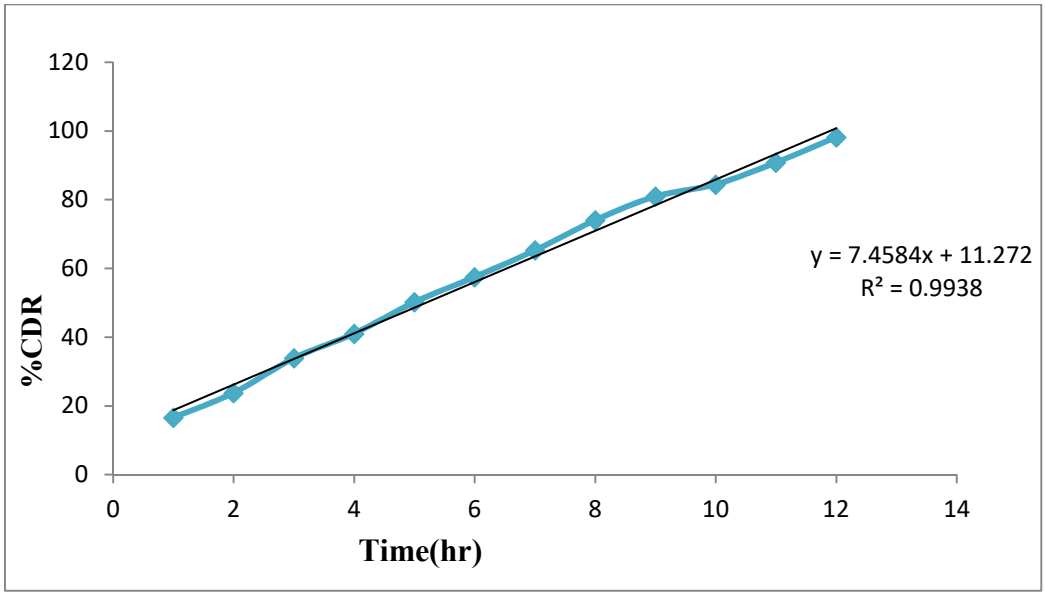

Fig.9: Graphical representation of Zero order release of Optimized formulation.

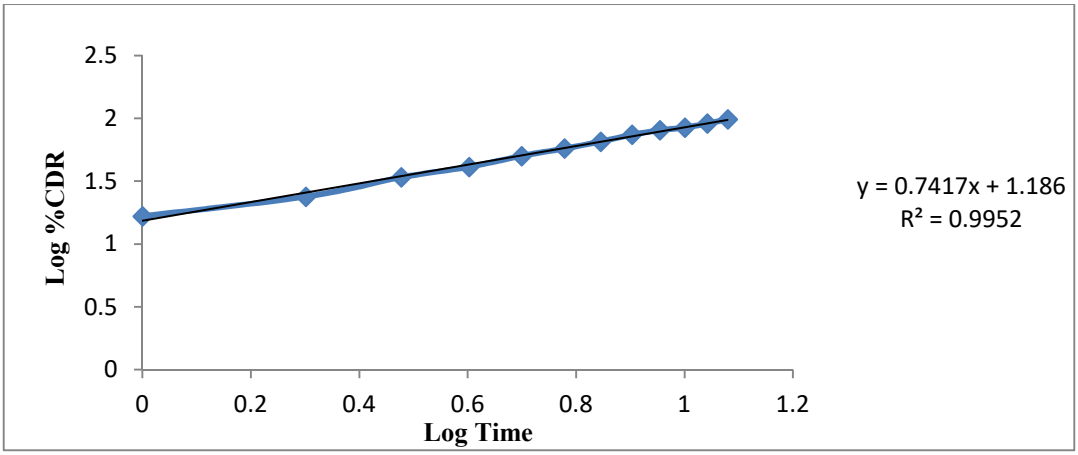

Fig.10: Graphical representation of Korsemeyer/ Peppas plot of Optimized formulation

DISCUSSIONS:

The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits. Tablet hardness varied as hydrophobic retardant was changed. Hardness of tablets containing carnauba wax was in range 5-8.5 kg/cm^2 (approx.) while that of tablets containing white paraffin wax was in range 6-8.5 kg/cm^2(approx.), cetyl alcohol showed hardness in range 3-6.5 kg/cm^2 and compritol888 showed hardness in range 4-8 kg/cm^2. The friability values of prepared tablets were shown in Table 7. Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion less than 1%. The drug content of the diluted samples of prepared floating tablets was estimated by UV visible spectrophotometer at λ_{max} 225nm. The drug contents of the tablets were shown in Table 7. The *in vitro* buoyancy studies in 0.1 N HCl (pH 1.2), revealed buoyancy variations for all the formulations (Table 8). Sodium bicarbonate was used as the effervescent base which generates carbon-di-oxide gas in the presence of hydrochloric acid present in dissolution medium. The gas generated is trapped and protected within the gel (formed by hydration of Methocel® (K15M), thus decreasing the density of the tablet. As the density of the tablet falls below 1 (density of water), the tablet becomes buoyant.

Swelling index was done which indicated that there was no significant swelling. All the formulations showed swelling only up to first 4 h due to presence of hydrophilic polymer from the results it was concluded that swelling increases with time because the polymer gradually absorbs water due to hydrophilicity and then constant results were obtained.

In vitro dissolution studies were performed in 0.1 N HCl (1.2 pH) and results depicted in figures. The drug release studies were performed for 12 hrs. The cumulative drug release of Venlafaxine HCl significantly decreased with increasing polymer concentration. Formulations S3 and S6 showed released 96.21, 98.20 respectively in 12hrs. Formulations S1, S2, S5, S8, and S11 showed more than 90% of drug release in just 8h. Formulations S4, showed less than 91% drug release in 12hrs. Finally a combination of Cetyl alcohol and HPMCK15M in the ratio 1:3in formulation S6 formulation showed 98.20% of drug release over a 12 hour period of time with lag time (39 sec) and total buoyancy time for than 12h. This formulation showed least possible lag time achieving the desired drug release compared to other combinations, so considered as optimized batch. To understand the rate and mechanism of drug release from optimized tablet formulation, dissolution data was fitted into different release kinetic models. The model that best fitted the release data for selected batch on the correlation coefficient value (R^2) obtained from various kinetic models. In vitro drug release profile from optimized formulation could be best expressed by Korsmeyere/Peppas equation and Zero order equations as plots showed highest linearity with R^2 value 0.9938 and 0.9938 respectively.

CONCLUSIONS:

In the present study, the drug of choice is Venlafaxine HCl, BCS Class I drug is highly soluble and highly permeable. Venlafaxine HCl was taken as drug of choice due to its less biological half-life (5hrs). Hence two to three times daily dose was needed for maintaining adequate plasma levels of the drug. Therefore different combinations of hydrophobic and hydrophilic polymers were used to sustain the release of venlafaxine HCl due to their non-toxicity, low cost, free availability and matrix forming property.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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