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FORMULATION, CHARACTERISATION AND *IN VITRO* DISSOLUTION STUDIES OF GASTRORETENTIVE FLOATING TABLETS BY MELT GRANULATION TECHNIQUE

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ABSTRACT

Gastro retentive drug delivery systems are one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract to control the gastric residence time. These are primarily controlled release drug delivery systems, which gets retained in the stomach for longer periods of time, thus helping in release of drug for the intended duration of time.

The aim of the present study is to formulate, characterize and perform *In vitro* dissolution studies of gastroretentive floating tablet Venlafaxine HCl. Venlafaxine HCl an anti depressant drug is a BCS class I drug having high solubility and high permeability. The main objective of the study was to prolong the drug release time by increasing the gastric residence time. Various formulations were developed by using varying ratios of Carnauba wax, White paraffin wax, Compritol ATO 888 and Cetyl alcohol as hydrophobic retardants and HPMC K100M as hydrophilic polymer. The FTIR and DSC data indicated that there were no interactions between the drug and polymers used.

The tablets were prepared by Hot melt granulation 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 white paraffin wax and hydrophilic polymer HPMC K100M in the ratio of 1:3 was the optimized formulation. The optimized formulation showed satisfactory sustained release of drug for about 12 hrs

. **Keywords: Gastro retentive, Anti-depressant, Melt granulation, Buoyancy**

INTRODUCTION

Depression is a mental disorder that is presented by depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Venlafaxine hydrochloride is a novel antidepresant belongs to serotonin-nor epinephrine reuptake inhibitor (SNRI). It is a BCS class I drug having high solubility and high permeability.

Oral controlled drug delivery system provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit. This system targets the delivery of a drug to a specific region within the GI tract for either 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 intention of adhering the dosage form to the inner wall of the stomach is to control the release of drug from the dosage form **[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 or 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, and HPMC K100M 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 75mg of Venlafaxine HCl were prepared by hot melt granulation method. Each floating tablet was prepared by employing sodium bicarbonate as a gas generating agent and water soluble polymer HPMC K100M as hydrophilic matrix (6). In order 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) 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 10mm standard flat – face punches on a multi punch tablet machine. Each tablet contains 75mg of Venlafaxine HCl and total tablet weight was kept constant at 300mg **(Table 1)**.

Table 1: Formulation of Venlafaxine HCl Floating tablets

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 K100M	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:

Visual inspection:

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 discolouration 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 and 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 Callipers. It is expressed in mm.

Friability: The friability test was carried out to evaluate the hardness stability instantly. The percent loss in weight or friability (f) was calculated by the formula given below **[9]**.

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

Uniformity of weight: The test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range **[10]**.

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. 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 **(Figure 1) [11]**.

In-vitro dissolution studies:

The release rate of Venlafaxine HCl floating tablets was determined using USP type II apparatus (paddle type). 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 membrane filter and sufficiently diluted. Absorbances of these solutions were measured at 225 nm using UV-visible spectrophotometer **(Figure 2)**.

Figure 1: In-vitro buoyancy of Venlafaxine HCl floating tablets

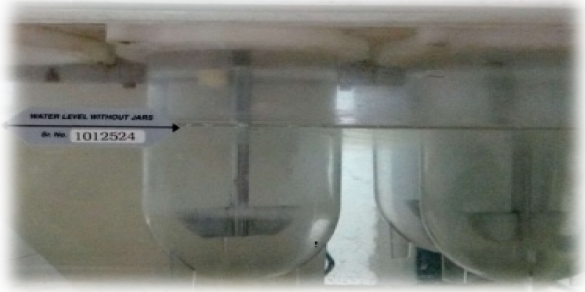

Figure 2: In vitro dissolution of Venlafaxine HCl floating tablets

Swelling index: The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulations was studied **[12]**.

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

FT-IR Study: The FT-IR spectra of drug, polymers and optimised 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.

Thermal Analysis:

DSC was performed using DSC calorimeter to study the thermal behaviour of pure drug, polymers and mixture of optimised 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 optimised formulation **[13]**.

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

$$A_t = A_0 - K_{0t}$$

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_0.

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.

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

Where,

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/ Peppas' 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.

$$M_t/M_a = Kt^n$$

RESULTS

Characterization of Venlafaxine Hydrochloride pure drug:

Venlafaxine hydrochloride pure drug was characterized for various organoleptic properties and solubility. The solubility studies were described in the **Table 2** given below. All values obtained were within the standards mentioned in IP 2016.

Drug-excipients interaction and identification:

Characterization of Active Pharmaceutical Ingredient (API):

UV spectroscopy (determination of λ (lambda) $_{max}$):

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 225nm.

Melting point:

The melting point determination of the drug sample was carried out by melting point apparatus as well as differential scanning calorimetry and found to be 216°C.

Drug-Polymer Compatibility study by Fourier Transform Infrared Spectroscopy:

Drug polymer interaction can be studied by FTIR analysis. The FTIR spectrum of Venlafaxine HCl showed a characteristic stretching band of O-H at 3349.0cm^{-1} , aromatic C=H stretching at 1613.3cm^{-1}, C-O stretching at 1513.3cm^{-1} and C-N stretching at 1177.8cm^{-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 **(Figure 3, 4)**.

Differential scanning Calorimetry Studies (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 **(Figure 5, 6)**.

Micromeritic studies:

Flow properties of Venlafaxine HCl:

The results of micromeritic properties are presented in the **Table 3**. Pure/plain Venlafaxine HCl exhibited angle of repose value 33° respectively indicated that the drug contains extremely 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 plain/pure drugs improved the flow properties as indicated by reduction in the values of angle of repose and Carr's index.

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.

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 4)**.

Post Compression Studies: Shown in **Table 5-8; Figure 7, 8**.

Table 2: Solubility studies of Venlafaxine HCl

Solvent	Venlafaxine HCl
Water	Soluble
Alcohol	Soluble
Acetic Acid	Soluble

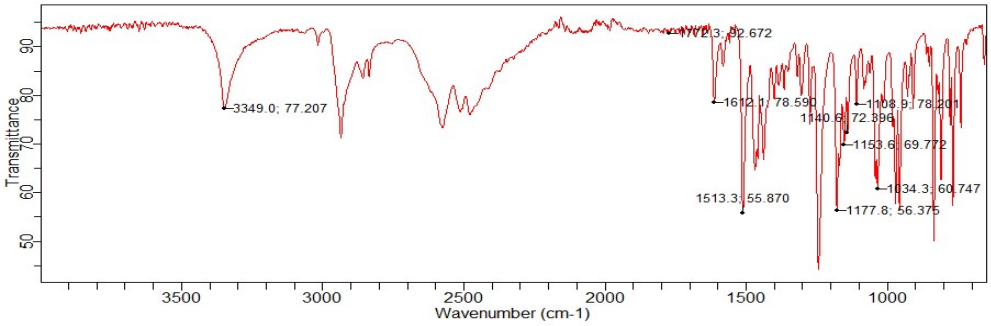

Figure 3: FTIR spectra of pure drug Venlafaxine HCl

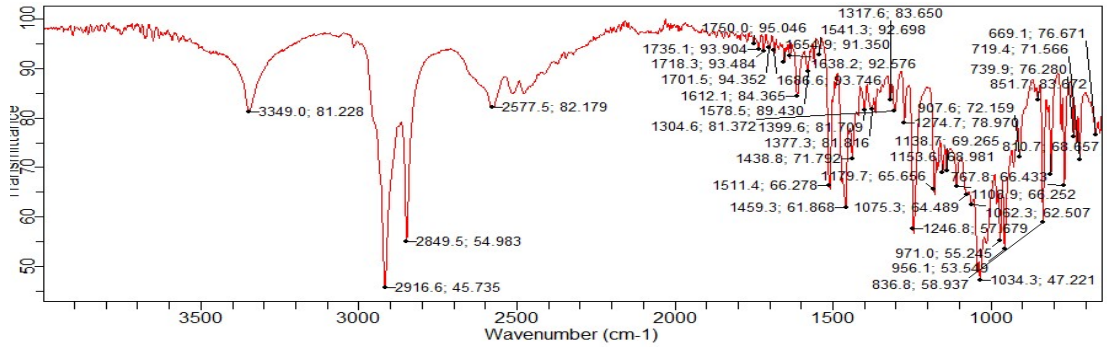

Figure 4: FTIR Spectra of Optimized formulation

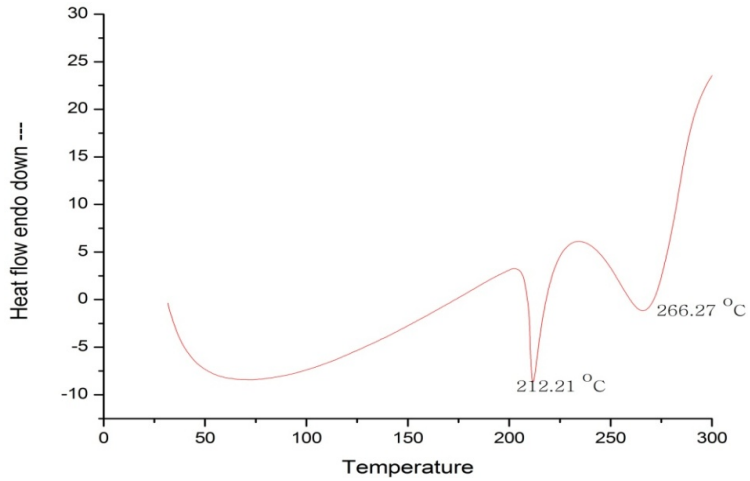

Figure 5: DSC curve of pure drug Venlafaxine HCl

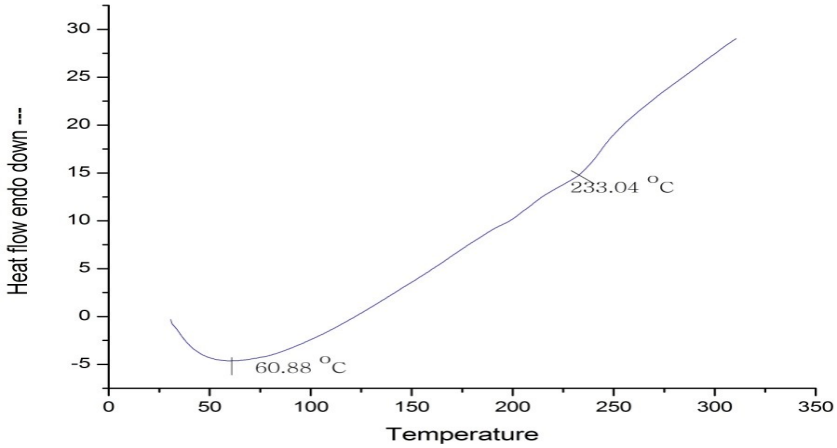

Figure 6: DSC curve of Optimised Formulation

Table 3: 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 Ø=tan^{-1}(h/r)	33°
04	Carr's index (%)	31.35
05	Hausner's ratio	1.45

Table 4: Micromeritic properties parameters of different formulations of Venalafaxine HCl

Formulation	Angle of repose θ = tan^{-1}(h/r)	Loose bulk density(LBD) (g/ml)	Tapped bulk density(TBD)	Carr's index (%)	Hausner's ratio
S1	26.76±0.25	0.325±0.002	0.408±0.01	19.63±3.88	1.25±0.065
S2	25.81±1.20	0.3458±0.01	0.398±0.009	13.11±2.64	1.15±0.035
S3	28.31±1.29	0.3123±0.01	0.378±0.01	17.46±1.71	1.21±0.025
S4	25.89±1.12	0.3321±0.005	0.4021±0.01	17.40±1.65	1.21±0.025
S5	27.92±0.90	0.2847±0.04	0.3324±0.05	14.35±1.4	1.16±0.025
S6	25.57±1.44	0.2552±0.07	0.3153±0.07	19.02±3.27	1.24±0.05
S7	27.21±0.19	0.3213±0.005	0.384±0.004	16.32±0.57	1.20±0.015
S8	26.12±0.89	0.3431±0.01	0.395±0.006	13.14±7.65	1.15±0.035
S9	28.24±1.22	0.3084±0.01	0.3571±0.03	13.63±2.12	1.16±0.025
S10	25.65±1.36	0.3212±0.005	0.4038±0.01	20.46±4.71	1.26±0.075
S11	28.32±1.30	0.3451±0.01	0.3895±0.001	11.40±4.35	1.12±0.065
S12	26.56±0.45	0.3328±0.005	0.3983±0.09	16.44±0.69	1.19±0.005

Table 5: Post Compression evaluation of different formulations of Venalafaxine HCl

Formulation	Uniformity of weight (mg)	Hardness Kg/cm^2	Friability (%)	Drug content (%)
S1	302±2.62	8.5±1.2	0.331±0.17	98.66±2.65
S2	301±1.62	8.0±0.7	0.332±0.17	97.23±1.22
S3	298±1.38	7.5±0.2	0.335±0.17	94.12±1.89
S4	302±2.62	8.5±1.2	0.331±0.17	92.13±3.88
S5	297±2.38	7.5±0.2	0.673±0.17	98.13±2.12
S6	300±0.63	8.0±0.7	0.333±0.17	96.31±0.3
S7	298±1.38	6.5±0.8	0.671±0.17	98.42±2.41
S8	296±3.38	7.0±0.3	0.337±0.16	95.12±0.89
S9	301±1.62	5.5±1.8	0.997±0.50	91.32±4.69
S10	300±0.63	6.8±0.5	0.333±0.168	94.23±1.78
S11	298±1.38	7.0±0.3	0.336±0.165	90.14±5.87
S12	300±0.63	6.5±0.8	0.667±0.166	92.32±3.69

All values are mean± standard deviation n;

Table 6: *In-vitro* buoyancy studies of Venlafaxine HCl

Formulation code	F.L.T (Sec) {buoyancy time}	T.F.T (hrs)	Swelling Index (%)
S1	40	>16	79.21
S2	129	<18	75.36
S3	37	<16	84.32
S4	44	>16	79.63
S5	15	>16	82.23
S6	11	<16	75.42
S7	20	>16	65.12
S8	62	>18	54.65
S9	26	<16	52.12
S10	45	>16	65.42
S11	52	<18	69.64
S12	19	<16	56.09

Table 7*: In-vitro* Dissolution Studies of Venlafaxine HCl Tablets

Formulation	1hr	2hr	3hr	4hr	5hr	6hr	8hr	10hr	12hr
S1	18.99	27.21	31.13	44.24	56.96	58.06	72.62	80.4	90.21
S2	33.2	38.56	63.46	98.33					
S3	23.8	34.93	43.86	53.1	62.4	77.86	84.52	92.56	98.3
S4	14.86	27.47	33.54	39.21	43.2	48.55	60.56	73.42	86.24
S5	16.47	24.29	31.27	43.21	52.46	54.16	64.13	76.06	82.89
S6	16.04	24.2	31.30	36.03	40.7	42.46	64.56	74.83	85.21
S7	27.43	45.8	49.1	58.06	59.2	65.41	71.54	77.73	88.21
S8	57.05	62.1	66.43	98.2					
S9	18.68	26.25	32.09	49.63	55.36	60.2	69.4	78.56	95.21
S10	20.07	30.79	36.66	39.3	47.9	49.7	60.36	64.72	75.62
S11	40.36	64.73	73.43	96.5					
S12	15.29	22.22	26.66	35.24	46.26	49.8	60.2	79.7	94.58

Table 8: Correlation coefficient values of S1 to S12 formulations

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

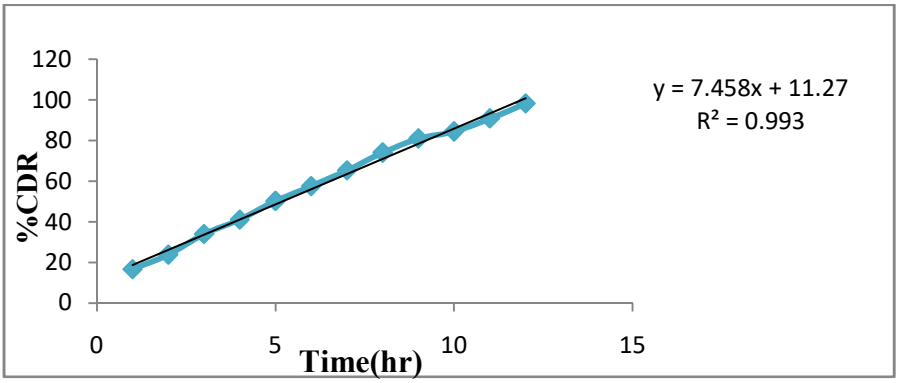

Figure 7: Graphical representation of Zero order release of Optimized formulation

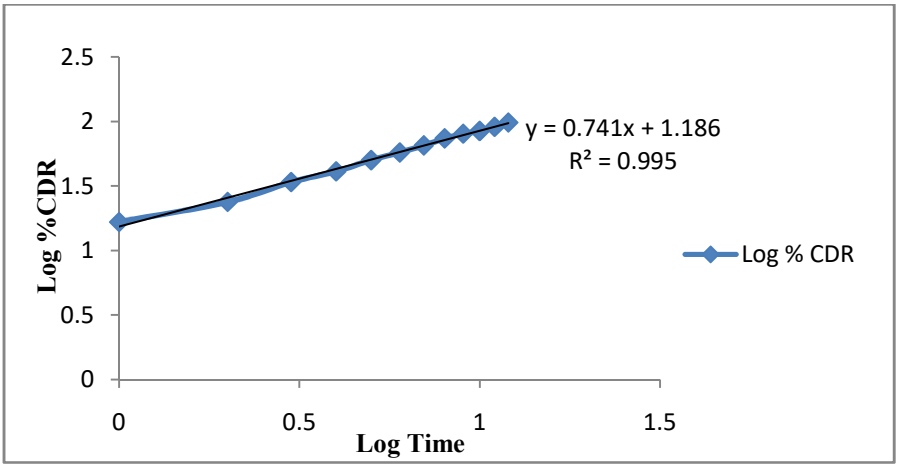

Figure 8: Graphical representation of Korsemeyer/ Peppas plot of Optimized formulation

DISCUSSION

Uniformity of weight:

The total weight of each formulation was maintained constant; the weight variations of the tablets were within the permissible limits.

Hardness:

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(approx.) and compritol888 showed hardness in range 4-8 kg/cm^2 (approx.).

Friability:

Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion less than 1%.

Drug content:

The drug content of the diluted samples of prepared floating tablets was estimated by UV-visible spectrophotometer at λ_{max} 225nm.

Evaluation of buoyancy of the tablets:

The in-vitro buoyancy studies in 0.1 N HCl (pH 1.2), revealed buoyancy variations for all the formulations. 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, K100M)), 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:

All the formulations showed swelling only up to first 4 hrs 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* drug release:**

In vitro dissolution studies were performed in 0.1 N HCl (1.2 pH). The drug release studies were performed for 12 hrs. The cumulative drug release of Venlafaxine HCl significantly decreased with increasing polymer concentration. Formulations S3, S9 and S12 released 98.3, 95.21, and 94.58 respectively in 12hrs. Formulations S2, S8, and S11 showed more than 90% of drug release in just 8h. Formulations S4, S5, S6, S7, and S10 showed less than 91% drug release in 12hrs. Finally a combination of White paraffin wax and HPMC K100M in the ratio 1:3 in formulation S3 formulation showed 98.3% of drug release over a 12 hour period of time with lag time (37 sec) and total buoyancy time less than 16h.

Kinetic analysis of release data

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 0.993 and 0.995 respectively.

CONCLUSION

In the present study, the drug of choice is Venlafaxine HCl, BCS Class I drug is highly soluble and highly permeable. The drug is highly soluble in water and sparingly soluble in organic solvents. The physical appearance was done by visual observation and found that Venlafaxine HCl is a white to off white crystalline powder. 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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