AJMHR
Asian Journal of Medical and Health Research
Journal home page: www.ajmhr.com

Formulation and Evaluation of Venlafaxine HCl Fast Dissolving Tablet By Using Natural Disintegrating Agent

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ABSTRACT

Fast dissolving tablets are gaining prominence as new drug delivery systems. Here, in this study venlafaxine HCl is taken as the model drug to convert in to fast dissolving tablet using combination of natural disintegrating agent. Venlafaxine HCl is commonly used as antidepressant, has poor bioavailability due to extensive first pass metabolism. The aim of the study is to fast relief against the depression. The fast dissolving tablet was prepared by various natural disintegrating agent like Treated agar and Isapghula husk powder. A 3^2 Full Factorial Design was applied to investigate the combine effect of Treated agar and Isapghula husk powder. Disintegrating time, wetting time and in vitro drug release taken as response variables. The prepared tablets were evaluated for in vitro dissolution, friability, hardness and weight variation. All blends were compatible by evaluating them on FTIR study. No drug-excipients interaction was found. Tablets were showing faster disintegration within seconds and Statistic analysis software showed that batch FB10 was found to be optimized as it had almost identical dissolution profile. Optimized batch FB10 was conducted at accelerated conditions for one month and it was found to be stable.

Keywords: Isapghula husk, Fast dissolving tablets, Venlafaxine HCl

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Received 16 February 2016, Accepted 3 March 2016

Please cite this article as: Patel HJ *et al*., Formulation and Evaluation of Venlafaxine HCl Fast Dissolving Tablet By Using Natural Disintegrating Agent. Asian Journal of Medical and Health Research 2016.

INTRODUCTION

Fast dissolving Tablets are disintegrating and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate .Delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. This tablet is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds.

Fast or mouth dissolving tablets have been formulated for pediatric, geriatric, and bedridden patients and for active patients who are busy and traveling and may not have access to water.

Limitations of Fast Dissolving Tablets:

The tablets usually have insufficient mechanical strength. Hence, careful handling is required. The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly[1].

In conventional ER and SR tablet due to high residence time there is chance of side effect like Nausea and Vomiting, so to overcome this effect fast dissolving tablet is advantageous.

The Ideal Characteristics of a Drug to Be Selected For FDT are Drug requires no water for oral administration for dissolve/disintegrate in mouth in a matter of seconds. Ability to permeate the oral mucosa and Low dose drugs preferably less than 50 mg. Drug should have good stability and solubility in water as well as in saliva[2,3,4]

Venlafaxine hydrochloride, commonly used as antidepressant, has poor bioavailability (45%) and short half life of 5 h, it shows 92% oral absorption and only 12.6% drug reaches to systemic circulation due to extensive first pass metabolism and gets converted into its active metabolite O – desmethyl venlafaxine. It has same neural activity like venlafaxine hydrochloride but differs in its half life which is 11 h. It act as hypertensive agent and also interferes with ejaculation in men. Furthermore drug Belongs to BCS class I which make is suitable for fast dissolving tablet.

So the aim of present study was to develop novel method of preparing compressed tablets for Venlafaxine hydrochloride which dissolves rapidly in mouth, using natural disintegrating agent.

MATERIALS AND METHOD

Venlafaxine HCl was Gift Sample from Zydus Cadila, Ahmedabad and other polymers was purchased from local market

Identification of drug

Description: White to off white powder.

Solubility:

Solubility of Venlafaxine Hydrochloride was found in distilled water and 6.8 pH phosphate buffer. Drug was dissolved in 10ml of the solvent up to saturation. The solution was sonicated on bath sonicator for 15 minutes, filtered, diluted if required. The amount of the drug dissolved was measured by using UV spectrophotometer.

Infrared spectroscopy:

The IR studies were carried out by the pressed pellet technique using a KBr press. Potassium bromide was taken and kept in a hot air oven for two hours for the removal of any moisture if present. The drug powder sample was mixed with dried KBr crystals and the mixture was pressed to form pellets using KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks.

Drug excipient compatibility study:

Drug excipient compatibility was studied by Infrared spectroscopy. The drug powder was mixed homogeneously with other formulation excipients. This homogeneous mixture was pressed to form pellets using KBr press. The prepared pellet was placed in the sample holder and kept in the instrument to record the IR peaks.

Calibration curve of Venlafaxine HCl in phosphate buffer pH 6.8:

- **Preparation of stock solution:**

10mg of Venlafaxine Hydrochloride was weighed accurately and transferred to 100ml volumetric flask. 10 ml phosphate buffer pH 6.8was added to dissolve it and final volume was made up to 100 ml with phosphate buffer pH 6.8 to prepare 100 µg/ml stock solution. These solutions were scanned in the spectrum mode from 400.0 to 200.0 nm. The maximum absorbance of Venlafaxine HCl was observed.

- **Preparation of calibration curve:**

The above stock solution was scanned for the maximum absorbance using UV Visible spectrophotometer. The λmax of Venlafaxine Hydrochloride in phosphate buffer pH6.8 was found to be 224 nm. The above stock solution (100µg/ml) was further diluted to get concentration in the range of 8-18 µg/ml. Absorbance of each solution was measured using UV-Visible spectrophotometer by putting reference standard of respective medium. The standard curve was generated for entire range of concentrations and the experiment was performed in triplicate.

Formulation using experimental design

Natural disintegrants were selected and then for these disintegrants the lower and upper limit for concentration of treated Agar and concentration of Isapghula Husk powder was determined by preparing different batches. After these lower and upper limits are determined then experimental design is applied to obtain an optimized batch. The results of different batches are fed in Design-Expert software and optimized batch is obtained. A 3 level 2 factors factorial design was employed to design fast dissolving tablet with the help of Design-Expert® 9.0 trial version software (Stat-Ease Inc., USA). The independent and dependent variables selected are as follows:

Table 1: Independent and Dependent Factors and levels

Independent Factors	Dependent Factors	Levels		
		-1	**0**	**1**
X_1:Concentration of Treated Agar	**R_1**:Disintegration time (Seconds)	3	4	5
X_2:Concentration of Isapghula Husk powder	**R_2**:In- vitro drug release(% CDR)	4	6	8

Table 2: Formulation of 3^2Factorial Design Batches F1-F9 by Direct Compression

Formulation Code	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Venlafaxine HCl	25	25	25	25	25	25	25	25	25
Treated Agar	3	4	5	3	4	5	3	4	5
Isapghula husk powder	4	4	4	6	6	6	8	8	8
MCC	20	20	20	20	20	20	20	20	20
Sucralose	2	2	2	2	2	2	2	2	2
Magnesium Stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Mannitol	44	43	42	42	41	40	40	39	38
Total	100	100	100	100	100	100	100	100	100

EVALUATION PARAMETERS OF TABLETS [5,6,7,8]

Pre-Compression Evaluation

The evaluations of Pre-compression studies of formulated fast dissolving tablets of Venlafaxine Hydrochloride were done as per standard procedures. The following parameters were evaluated.

Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve #20) in to a measuring cylinder and the initial volume was noted, it is bulk volume. The bulk density is calculated by given formula,

$$\text{Bulk density } (\rho b) = \text{Mass of the powder (M)} / \text{Bulk volume (VB)}$$

Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 100 times. It is expressed by given formula,

Tapped density (ρT) = Mass of the powder (M) / Tapped volume (VT)

Carr's Index:

It is the simple test to evaluate the bulk density and tapped density of a powder and the rate at which it packed down. It is expressed by the given formula,

Carr's Index (%) = [(Tapped density – Bulk density) / tapped density x 100]

Table 3: Flow Property according to Carr's Index

Sr. No.	Carr's Index	Flowability
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair to passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	> 40	Very very poor

Hausner's Ratio:

It is the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density / Bulk density

Angle of repose:

Angle of repose of powdered blend was determined by the funnel method. The accurately powdered blends were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powdered blend was allowed to through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated by using the following formula,

$$\text{Tan } Ø = h/r$$

h = height of the powder cone,

Ø= angle of repose,

r = radius of the powder cone

Table 4: Relationship between Angle of Repose and Powder Flow

Sr. No.	Angle of Repose (θ)	Flow ability
1.	<20	Excellent
2.	20-30	Good
3.	30-34	Passable
4.	>34	Very Poor

Post-compression evaluation [9,10,11,12]

The prepared tablets can be evaluated for various official and non-official specifications.

Thickness:

The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier caliper. The average values were calculated.

Hardness Test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. "Hardness factor", the average of the four determinations, was determined and reported. The force was measured in kilograms per centimeter square.

Friability Test:

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Permitted friability limit is 1.0 %. Roche friabilator was used to measure the friability of the tablets. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. The percent friability was determined using the following formula;

$$\text{Friability} = (W1 - W2)/ W1 \times 100$$

W1 = weight of the tablet before test,

W2 = weight of the tablets after test.

Weight Uniformity Test:

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The percent deviation was calculated using the following formula.

$$\text{Percentage Deviation} = \frac{\text{Individual weight - Average weight}}{\text{Average weight}} \times 100$$

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limit of 7.5% is allowed as the tablet weighs 200 mg. Corrections were made during the compression of tablets to get uniform weight.

Content Uniformity Test:

Three tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were

diluted up to the mark with phosphate buffer (pH 6.8) solution. The contents were shaken periodically and kept for 24 hours for solvation of drug completely. The mixtures were filtered, appropriately diluted, and absorbance was measured at λmax 224 nm against blank reference. The drug content in each tablet was calculated.

In- vitro Disintegration Time:

In-vitro Disintegration times for fast dissolving tablets were determined using USP tablet disintegration apparatus with phosphate buffer of pH 6.8 as medium. The volume of medium was 900 ml and temp was 37± .5 °C. The time in seconds taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured.

Wetting Time:

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure. Two circular tissue papers of 10 cm diameter are placed in a Petri dish having the same inner diameter. Ten ml of phosphate buffer solution, 6.8pH is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time.

In-vitro Dissolution test[13]

Percent drug release of venlafaxine hydrochloride fast dissolving tablets was determined by USP dissolution test apparatus using paddle method. The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 at 37 °C ± 0.5 °C at 50 rpm. A sample of 5 ml solution was withdrawn from dissolution apparatus at regular interval of 30 s. The same quantity of sample was replaced with fresh dissolution medium. The samples were filtered through 0.45 μm membrane filter. Absorbance of these samples was analyzed at λ_{max} 224 nm using UV–visible spectrophotometer.

Stability studies[13]

The ICH Guidelines have established that long term stability testing should be done at 25°C±2°C / 60%±5% RH; stress testing should be done at 40°C±2°C / 75%±5% RH for 6 months. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition at 30°C±2°C /75%±5% RH. Table 5 shows different temperatures and period of stability testing.

Table 5: ICH guidelines for stability study

Study	Storage condition	Minimum time period covered by data at submission
Long term	25°C±2°C / 60%±5% RH	12 months
Intermediate	30°C±2°C / 65%±5% RH	6 months
Accelerated	40°C±2°C / 75%±5% RH	3 months

RESULTS AND DISCUSSION

In the present study different formulation with variable concentration of Natural Disintegrating agent were prepared and evaluated for physic-chemical parameters; in vitro release/dissolved studies and stability studies.

Pre-formulation Studies of Pure Drug Venlafaxine HCl:

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination and standard curve.

Identification of drug

Solubility: Solubility was determined in distilled water and pH 6.8 Phosphate buffer solution.

Table 6: Solubility study of Venlafaxine HCl

Medium	Solubility
Water	Freely soluble (412 mg/ml)
pH 6.8 Phosphate buffer	Freely soluble (397 mg/ml)

Solubility study of Venlafaxine HCl showed that Venlafaxine HCl is freely soluble in water and phosphate buffer pH 6.8.

Drug–Excipients Compatibility Studies:

The IR study was carried out by pressed pellet technique. For investigation of any chemical interaction between added excipients and Venlafaxine HCl in the formulated products, the FTIR of pure Venlafaxine HCl and Venlafaxine HCl + Natural Disintegrating agents (excipients) were recorded. It was observed however, that all the characteristic peaks observed for both pure drug and excipients remained unchanged. This observation ruled out of the possibility of chemical interaction between the drug and excipients during direct compression method to form the tablets.

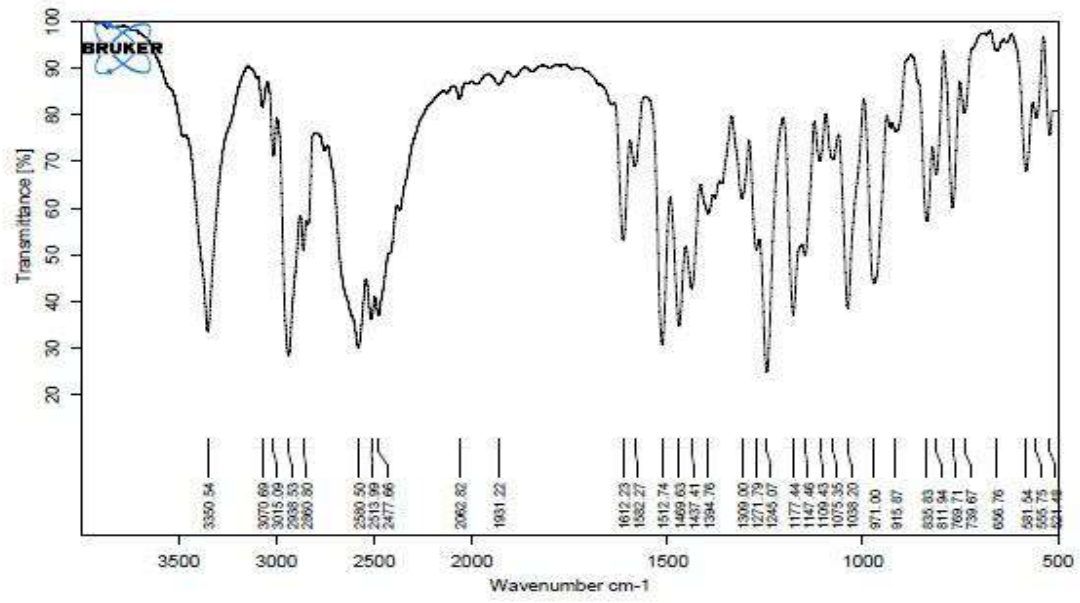

Figure 1: IR spectra of Venlafaxine hydrochloride

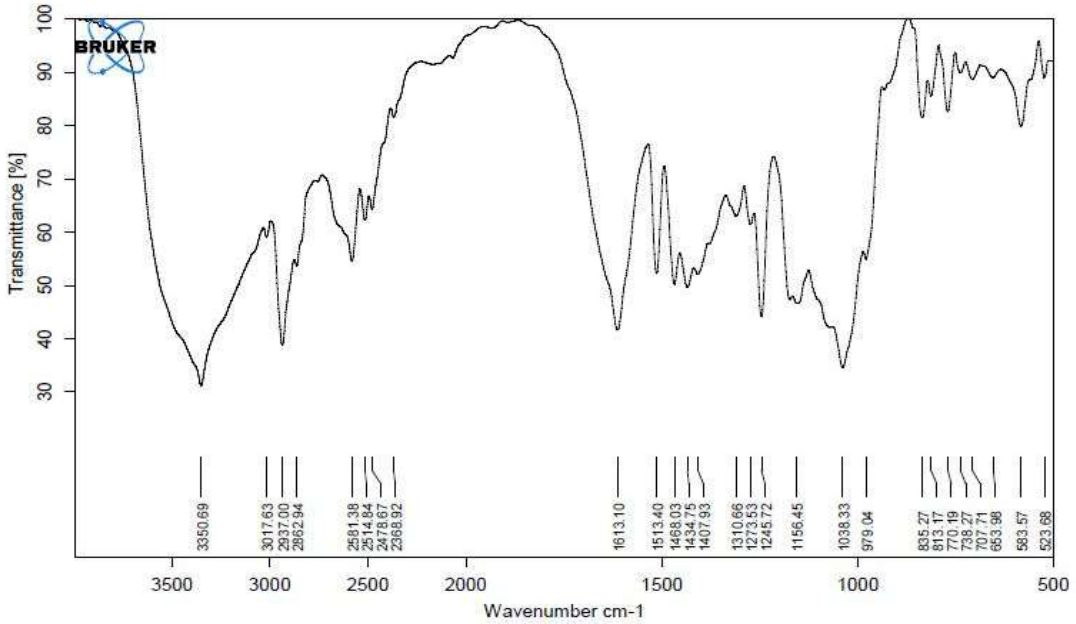

Figure 2: IR spectra of physical mixture

Table 7: FTIR peaks of pure Venlafaxine HCl and physical mixture

Sr. No	Functional group	Range IR peak(cm-1)	IR peak of pure Venlafaxine HCl	IR peak of physical mixture	Observation
1	OH	3300-3400	3350.59	3350.69	No interaction
2	C_6H_5	1500-1600	1512.74	1530.40	No interaction
3	Aliphatic CH	2800-3000	2938.53	2937.00	No interaction
4	C-O-C	1000-1200	1147.46	1156.45	No interaction

Frequencies of principal peak in IR spectra of physical mixture of drug and excipients were nearly similar to the principal peak of pure drug. This indicated that there was no incompatibly between drug substances and excipients used in formulation.

Calibration Curve of Venlafaxine HCl in phosphate buffer pH 6.8:

The calibration data had correlation coefficient of 0.993.

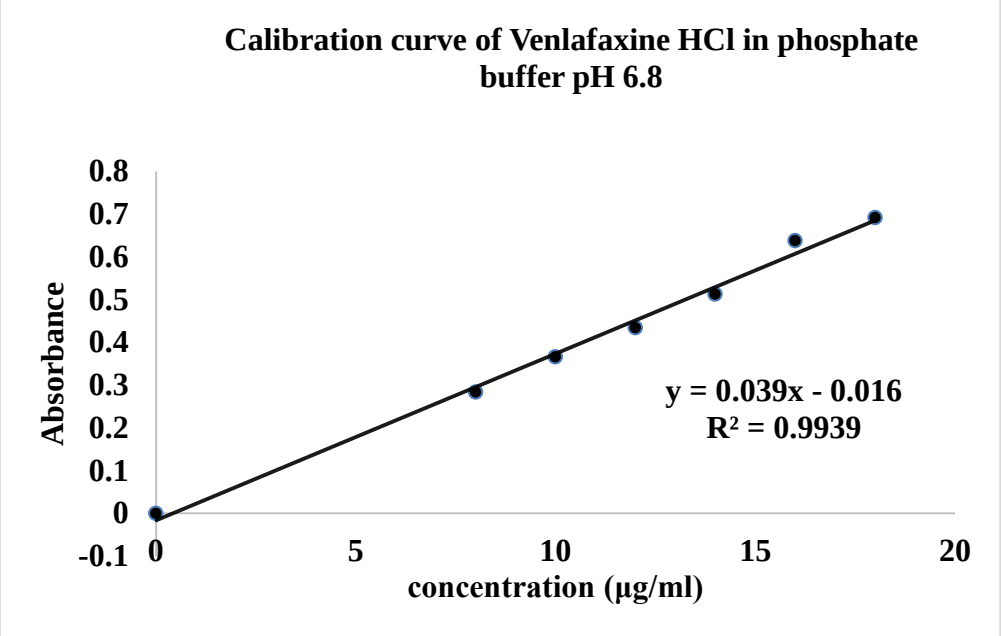

Figure 3: Standard Calibration Curve of Venlafaxine HCl in pH 6.8 buffer.

Evaluation of Final Batches (3^2Full Factorial Design):

Table 8: Preformulation Study of Final Batches F1-F9

Batch	Bulk Density (g/cm^3) Mean±SD	Tap Density (g/cm^3) Mean±SD	Carr's Index (%) Mean±SD	Hausner's ratio Mean±SD	Angle of repose Mean±SD
F_1	0.564±0.007	0.641±0.01	12.05±0.384	1.14±0.005	26.76±0.659
F_2	0.564 ±0.0071	0.688±0.007	18.08±1.45	1.21±0.25	28.94±0.19
F_3	0.581±0.007	0.683±0.007	14.98±0.83	1.175±0.011	25.65±0.827
F_4	0.59±0.004	0.6786±0.01	12.65±1.88	1.143±0.025	27.55±0.34
F_5	0.57±0.015	0.706±0.015	18.79±3.76	1.23±0.05	26.771±0.89
F_6	0.589±0.009	0.699±0.008	15.71±0.589	1.18±0.007	28.29±0.678
F_7	0.55±0.009	0.643±0.005	14.46±1.01	1.16±0.011	25.74±0.72
F_8	0.55±0.006	0.654±0.005	15.51±0.875	1.18±0.013	25.85±1.15
F_9	0.544±0.003	0.666±0.004	18.33±0.76	1.22±.009	27.55±0.355

The results obtained which lies in the acceptable range and from the data it was concluded that powder blend had good to acceptable flow property and compressibility. There was a minimal difference between results of the batches.

Table 9: Diameter, Thickness, Hardness, Friability &Weight variation, of Final Batches F1-F9

Batch	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2) Mean±SD	Friability(%) Mean±SD	Weight variation Mean±SD
F_1	6	2.5	2.9±0.057	0.42±0.049	100.78±2.79
F_2	6	2.5	3.1±0.25	0.405±0.03	99.64±2.85
F_3	6	2.5	2.97±0.058	0.398±0.028	99.64±3.38
F_4	6	2.5	3.17±0.058	0.357±0.058	101.16±2.96

F_5	6	2.5	3.167±0.057	0.496±0.015	100.85±3.61
F_6	6	2.5	3.23±0.057	0.58±0.105	99.49±2.44
F_7	6	2.6	2.97±0.15	0.53±0.02	98.62±2.57
F_8	6	2.4	3.2±0.1	0.479±0.029	100.45±2.43
F_9	6	2.6	3.43±0.057	0.397±0.028	99.75±2.22

Hardness and Friability of the tablets

The hardness of all the formulations was checked using Monsanto Hardness Tester, The average hardness of all the batches was in the range of 2.9 ± 0.057 to 3.43 ± 0.057 kg/cm^2. The lower standard deviation values indicated that the hardness of all the formulations possess good mechanical strength with sufficient hardness.

The friability test is designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping. A number of tablets were weighed and placed in Friabilator where they were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After a given number of rotations the tablets were weighed, and the loss in weight indicates the ability of the tablet to withstand wear and tear. The results are given in Table 9. The percentage friability for all the formulations lies in the range of 0.357% to 0.58%, which was found to be within limit (Not More Than 1%).

Weight Variation Test

All the formulations passed weight variation test as the % weight variation was within the pharmacopoeia limits of ± 10%. It was found to be from 98.62 to 101.16%. None of the formulations were exceeding the limit ± 10% specified by USP .Thus all the formulations were found to comply with the USP standard.

Table 10: Disintegration Time, Wetting Time, Water Absorption Ratio, Dispersion Time & % Drug Content of Batches F1-F9

Batch	Disintegration time (sec) Mean±SD	Wetting time (sec) Mean±SD	Water absorption ratio (%) Mean±SD	Drug content Mean±SD
F_1	52±1.52	40±1.52	31.393±0.63	94.87±0.395
F_2	40.32±0.577	31.33±1.52	41.55±1.473	96.55±0.79
F_3	39.33±1.52	27±2.52	38.04±0.457	97.25±0.198
F_4	44.66±2.08	37.31±0.578	36.41±2.8	97.95±1.188
F_5	37±1.53	29±1.52	50.53±2.23	98.378±0.20
F_6	34.67±0.58	28±1.52	43.39±0.72	99.35±0.79
F_7	36±2.51	34.33±1	51.52±0.056	99.07±0.40
F_8	30±2.08	25±0.59	52.46±2.52	99.495±0.19
F_9	34.33±1.53	28.66±1.53	47.25±0.68	97.67±0.396

In vitro Disintegration Test

The average in vitro disintegration time for all the formulations lies within the range of 30±2.08seconds to 52±1.52seconds. Here, formulation F8 containing combination of 4% Treated Agar & 8% Isapghula husk powder showed lowest disintegration time.

Wetting Time and Water Absorption Ratio

Wetting is closely related to inner structure of tablets. The wetting time in different formulations vary according to the ability of disintegrants for swelling and capacity of absorption of water. It was in the range of 25±0.59seconds to 40±1.52seconds. Water absorption ratio, which is important criteria for understanding the capacity of disintegrates to swell in presence of little amount of water, was calculated. It was found in the range of 31.393 ± 0.63 to 52.46 ± 2.52.

Drug Content Estimation

The drug content values for all the formulations are in the range of 94.87 ± 0.395 to 99.495 ± 0.19.

In-vitro Dissolution test parameters

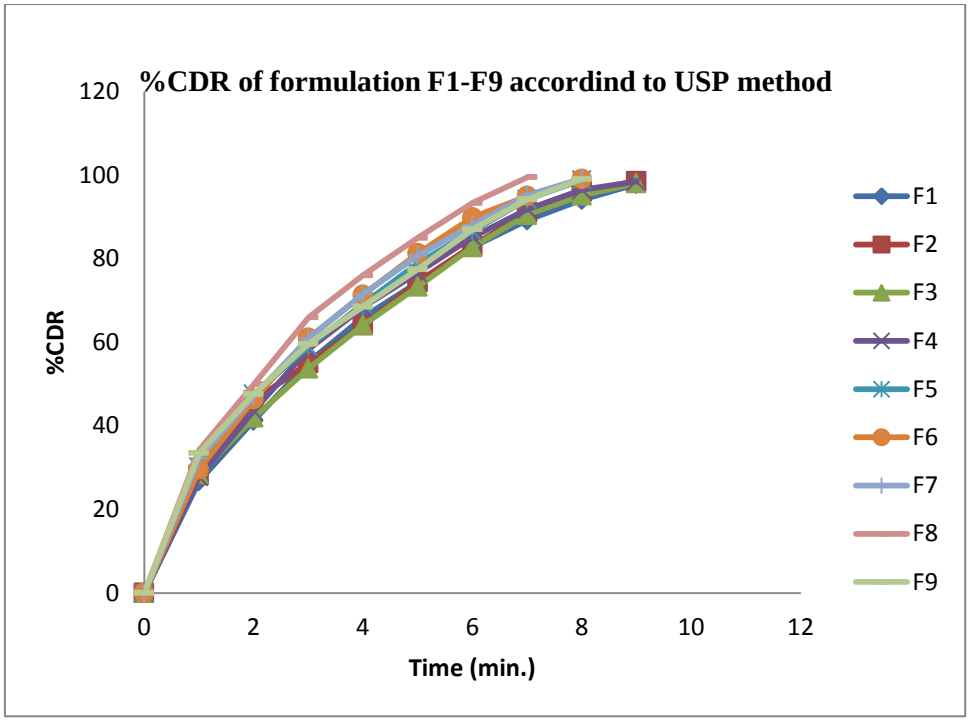

Figure 4: % Cumulative Drug Release of Formulations F1-F9 According to USP Method

In vitro Drug Release Studies

Formulation which having a lower disintegration time are best preferred for the formulation of fast dissolving tablets. The samples were withdrawn at specified time intervals and analyzed by UV method. Cumulative % drug release was calculated on the basis of amount of Venlafaxine HCl present in the respective formulation. The percentage cumulative drug release of fast dissolving formulations of Venlafaxine HCl was plotted against time

According to USP Method the highest drug release in lowest time (7 min) showed in formulation F8 was (99.50%).

Statistical Analysis of Experimental Data by Design Expert 9.0 Software

In this study, amount of Treated Agar and Isapghula Husk powder were chosen as the independent factors. The dependent variables included Disintegration time and Wetting Time. The effect of formulation factors on the response variables were statically evaluated by applying ANOVA using Design-Expert® 9.0. The design was evaluated using a quadratic model, which bears the form of the equation

$$Y= b0 + b1\ X1+ b2\ X2+ b12\ X1\ X2+ b11\ X12+ b22\ X22$$

Where Y is the response variable, b_0 the constant and b_1, b_2, b_{12}, b_{11}, b_{22} are the regression coefficient. X_1 and X_2 stand for the main effect, X_1X_2 are the interaction terms that shows how the response changes when two factors are simultaneously changed. X_1^2 and X_2^2 are quadratic terms of the independent variables to evaluate the nonlinearity.

Response 1 – disintegration time

Polynomial equation for disintegration time

$D.T = +168.889-45.750*X_1-8.583*X_2+1.375*X_1*X_2+4.167*X_1^2+0.042*X_2^2$

Table 11: ANOVA for disintegration time

Source	Sum of Squares	Df	Mean Square	F Value	p- value prob>f	significant
Model	329.36	5	65.87	28.80	0.0097	
A - conc. of Treated Agar	104.17	1	104.17	45.55	0.0066	
B - conc. Of Isapghula Husk powder	160.17	1	160.17	70.03	0.0036	
X_1X_2	30.25	1	30.25	13.23	0.0358	
X_1^2	34.72	1	34.72	15.18	0.0300	
X_2^2	0.056	1	0.056	0.024	0.8860	
Residual	6.86	3	2.29			
Cor Total	336.22	8				

$R^2 = 0.9796$, R^2 (adjusted) = 0.9456, R^2 (predicted) = 0.8176

The Negative co-efficient of variables X_1 and X_2 i.e. Treated Agar and Isapghula Husk powder in case of response i.e. disintegration time indicated that, as the amount of Treated Agar and Isapghula Husk powder was increase, the disintegration time was found to decrease. Both variables have p value less than 0.05 ($p<0.05$) which was considered as significant.

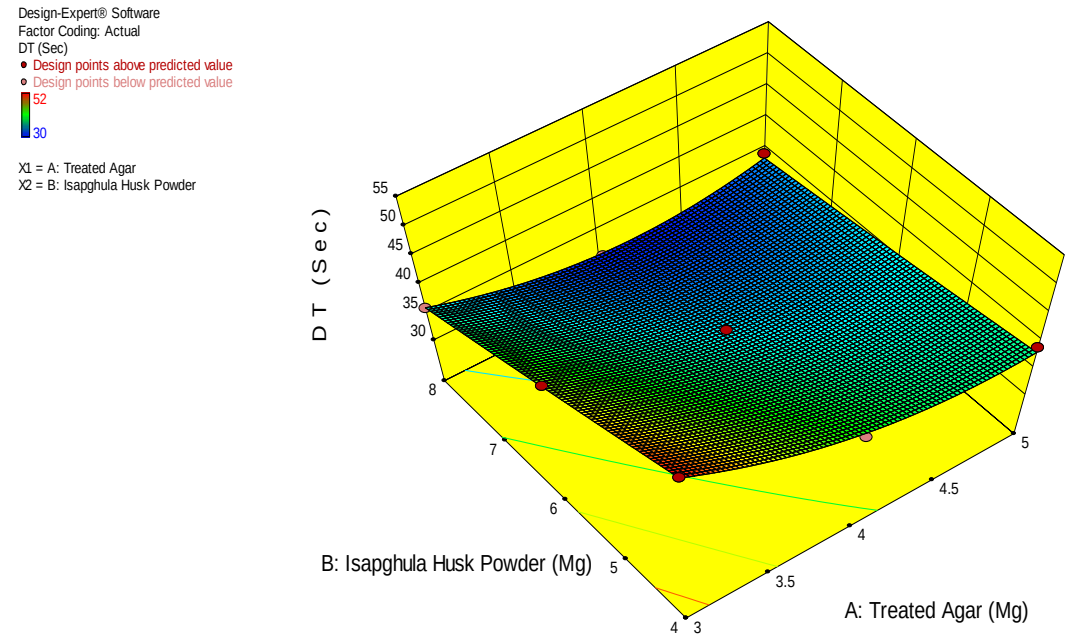

Figure 5: Response surface plot showing the effect of amount of Treated Agar (X1) and Isapghula Husk Powder (X2) on the response Disintegration Time (Y1)

Response 2 – wetting time

Polynomial equation for disintegration time

Wetting time = $+133.333-41.917*X_1-2.917*X_2+0.875*X_1*X_2+4.000*X_1^2-0.125*X_2^2$

Table 12: ANOVA for wetting time

Source	Sum of Squares	Df	Mean Square	F Value	p- value prob>f	Significant
Model	195.58	5	39.12	26.57	0.0109	
A - conc. of Treated Agar	130.67	1	130.67	88.75	0.0025	
B - conc. of Isapghula Husk powder	20.17	1	20.17	13.70	0.0343	
X_1X_2	12.25	1	12.25	8.32	0.0633	
X_1^2	32.00	1	32.00	21.74	0.0186	
X_2^2	0.50	1	0.50	0.34	0.6010	
Residual	4.42	3	1.47			
Cor Total	200.00	8				

$R^2 = 0.9779$, R^2 (adjusted) = 0.9411, R^2 (predicted) = 0.7367

The Negative co-efficient of variables X_1 and X_2 i.e. Treated Agar and Isapghula Husk powder in case of response i.e. wetting time indicated that, as the amount of Treated Agar and Isapghula Husk powder was increase, the wetting time was found to decrease. Both variables have p value less than 0.05 ($p<0.05$) which was considered as significant.

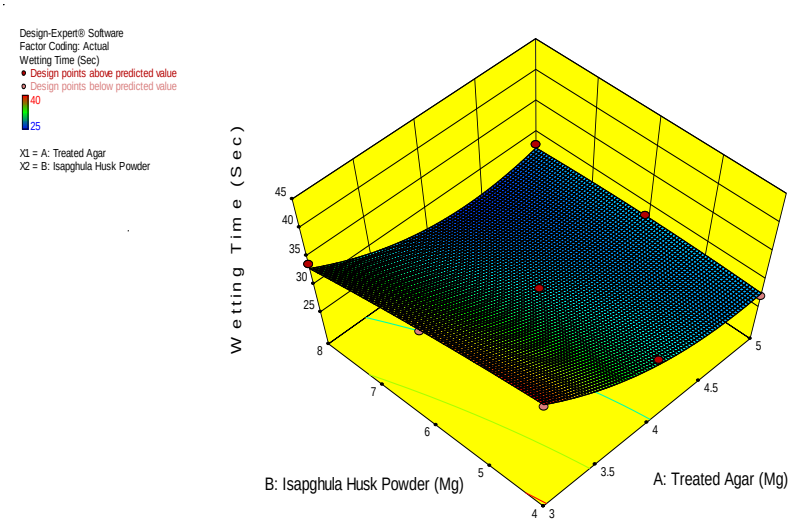

Figure 6: Response surface plot showing the effect of amount Treated Agar (X1) and Isapghula Husk Powder (X2) on the response Wetting Time (Y2)

Validation of Optimized batch

Formulation containing 4.142 mg of Treated Agar and 8.00 mg of Isapghula Husk Powder was found to maximum desirability found in the experimental region of the overlay plot. So, it was selected as the optimized batch.

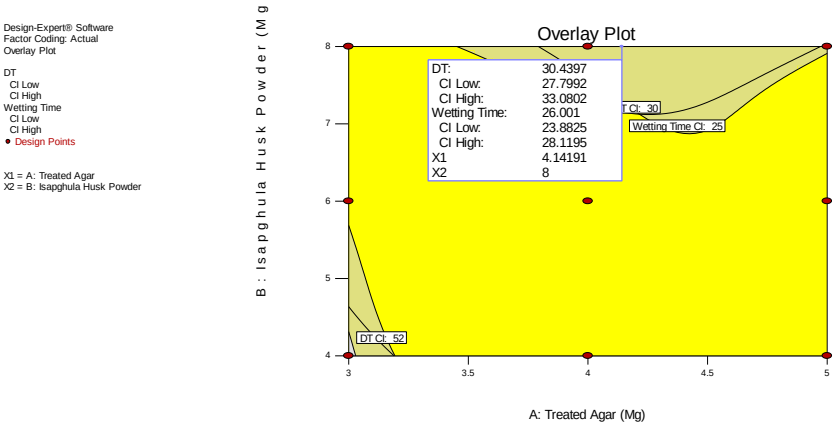

Figure 7: Overlay Plot showing combined effects of Treated Agar (X1) and Isapghula Husk Powder (X2) on Disintegration and Wetting Time (Y1, Y2)

Table 13: Composition of Optimized Formulation

Ingredients	Quantity (mg)
Venlafaxine HCl	25
Treated Agar	4.14
Isapghula Husk Powder	8.00
MCC	20
Sucralose	2
Mg. Stearate	1
Talc	1
Mannitol	38.86
TOTAL	100

Table 14: Comparison chart of predicted and experimental values for optimized formulation

Dependent Variables	Optimized Formulation		
	Predicted Value	Experimental Value	Residual
Disintegration Time (Sec)	30.43	29.67±2.08	0.76
Wetting Time (Sec)	26.00	25.33±0.58	0.67

The results demonstrated a good relationship between the predicted and experimental values, confirming the validity of the model.

Stability Study

Stability study was carried out at 40 ± 2^{o}C and 75 % RH and at Room temperature for one month storage condition. Optimized Batch was taken for stability study and various parameters were compared for stability study.

Table 15: Comparison of Various Parameters for Stability Study

Evaluation Parameter	Initial	After one month	
		Room Temp.	Accelerated
Disintegration Time (sec)	30±2.08	28.66±1.16	26.33±0.567
Wetting Time (sec)	25±0.59	23.67±0.578	22±1
Hardness	3.2±0.1	3.167±0.059	3.03±0.068
%Friability	0.479±0.029	0.55±0.039	0.5841±0.022
Drug Content	99.495±0.19	98.70±0.33	97.77±0.43

Note: Values are mean value of 3 observation (N=3), and values in parenthesis are Standard deviation (± SD)

Table 16: % CDR Profile of optimized Batch for Stability Study According to USP Method

Time (min)	Initial	After one month	
		Room Temp.	Accelerated
1	34.19±0.424	33.33±0.224	31.728±0.64
2	49.93±0.712	49.447±0.294	46.79±1.39
3	65.92±0.497	63.513±0.748	61.05±1.019
4	76.01±0.729	74.17±0.36	73.297±0.51
5	84.97±0.648	83.67±0.45	81.48±0.59
6	93.319±1.2	91.05±0.99	90.157±1.44
7	99.50±0.216	98.66±0.181	97.535±0.29

Note: Values are mean value of 3 observation (N=3), and values in parenthesis are Standard deviation (± SD)

CONCLUSION

The aim of the present work was to formulate and evaluate fast dissolving tablets of Venlafaxine HCl, a novel drug for depression. Total 9 batches were prepared by using different concentrations 3^2 Full factorial design was applied to check the combination effects of disintegrants. Tablets were prepared and evaluated for the all evaluation parameters. Statistical Analysis of the experimental model by Design Expert 9.0 software was done using

Disintegration time and Wetting time as dependent variables. New Batch was optimized by the statistical analysis. There was no significant difference between predicted values and experimental values. Optimized formulation was having 4.14 mg Treated Agar and 8 mg Isapghula Husk Powder. The optimized formulation was also subjected to Stability study at accelerated conditions and proven to be stable for different evaluation parameters. From the results it was concluded that Fast dissolving Tablets of Venlafaxine HCl were prepared and optimized successfully to achieve desired characteristics for immediate relief in depression.

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