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Formulation and Evaluation of Hot-melt moulded extended- release tablet of Venlafaxine HCl.

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ABSTRACT

Objective: To prepare and optimize hot melt moulded extended-release of Venlafaxine HCl tablet capable of drug release for 12 hrs using suitable experimental design.
Method: Initially preliminary trial batch was carried out for the selection of hydrophobic base, effect of HLB modifier and channeling agent and also for the selection of their relative quantity for preparation of Venlafaxine HCl extended-release tablet. Stearic acid selected as base, PEG 6000 as HLB modifier, NaCl as channeling agent used with their suitable quantity. For the preparation of Venlafaxine HCl extended-release tablet by hot melt moulding method.
Result and discussion: Identification and compatibility study of drug and excipients were carried out using melting point FTIR and DSC study. Identification proved the drug authentication and compatibility studied proved that Venlafaxine HCl was compatible with selected excipients. Venlafaxine HCl showed λmax 225nm in 0.1N HCl. Hydrophobic base (stearic acid), PEG 6000, NaCl found to be providing the desired result. Result of drug release depend on the concentration of PEG and NaCl % drug release at 15min (Y1) and % drug release at 540 min (Y2) response. Drug release 19.297% at 15 min and drug release 87.526 % at 540 min which was desired for extended-release tablet of venlafaxine HCl.

Keywords: Venlafaxine HCl, Channeling agent, HLB modifier.

INTRODUCTION

Depression is a mood disorder characterized by a persistent feeling of sadness, loss of interest, exhaustion, worthlessness, helplessness, and hopelessness. It is a disease that affects the body, mood, and thoughts, and it affects how one eats and sleeps, how one feels about oneself, and how one thinks about things.(1,2)Venlafaxine hydrochloride is a new third-generation antidepressant that works primarily by inhibiting serotonin and noradrenaline reuptake. It is hypothesized that pharmacologic behaviour at these receptors is linked to the numerous anticholinergics, sedative, and cardiovascular symptoms observed in other psychotropic medications.(3,4)A dosage form that provides for at least a twofold decrease in dosage duration as compared to the same drug in an immediate-release (conventional) dosage form. Control-release, sustained- release, and long-acting drug products are examples of extended-release dosage types. (5) An extended-release drug product's goal is to have a longer therapeutic benefit while minimizing unintended side effects caused by fluctuating plasma drug levels. Ideally, the extended-release drug product can release the drug at a steady or zero-order rate that is independent of pH and ionic content in the entire gastrointestinal tract.(6) The drug is quickly ingested after release from the drug product, and the drug absorption rate can obey zero-order kinetics, equivalent to an intravenous drug infusion. The drug product is often formulated in such a way that the rate of systemic drug absorption is restricted by the rate of drug release through the drug delivery mechanism. (7) Unfortunately, most extended-release drug products that have zero-order kinetics Invitro do not have zero-order drug absorption when administered in vivoThe loss of zero-order drug absorption from these extended-release drug products following oral administration may be attributed to a series of unforeseeable events occurring in the gastrointestinal tract during absorption. (8,9) Extended-release oral drug products last longer in the GI tract than traditional, immediate-release drug products designed for fast absorption. Thus, drug release from an extended-release drug product is more influenced by the structure and physiology of the gastrointestinal tract

and its contents than drug release from an immediate-release oral drug product.(10) The physiologic features of the GI tract, such as differences in pH, blood flow, GI motility, the presence of food, enzymes, bacteria, and so on, influence the location of the extended-release drug product within the GI tract and can affect the drug release rate from the product.(11)Hot-melt refers to the process of using heat to melt a base. The hot-melt moulding method canbe used as a platform technology for the sustained release formulations of highly soluble drugshaving poor flow and compression properties. (12,13)

MATERIALS AND METHODS

Chemicals

Venlafaxine HCl was procured as a gift sample from Cadilla Healthcare Limited. Stearyl alcohol, Cetyl alcohol, and Stearic acid were purchased from Mody Chem. Cetostearyl alcoholand Sodium Chloride (NaCl) were purchased from Loba Chemie Pvt. Ltd.. Beeswax and Polyethylene glycol (PEG 6000) were purchased from HiMedia Laboratories Pvt. Ltd.

METHODOLOGY

Selection of experimental protocol

There were many formulation variables, which affect the properties of extended- release tabletwhich were identified and studied. Two factors were observed to mainly affect drug release from the moulded extended-release tablet. One of the factors from them is % of PEG and another factor is % of NaCl, which appeared to effect dissolution. 1. Percentage of PEG 6000

Percentage of NaCl. Design of experiments

In order to investigate the effect of independent variables on dependent variables, 3^2 full factorial design was adopted.[14] The independent and dependent variables were given in Table

1. In mathematical approach, experimental response Y can be represented by a quadratic equation of response surface:

$$Y = \beta0 + \beta1X1 + \beta2\ X2 + \beta12\ X1X2 + \beta11\ XXXX^{\ 2} + \beta22\ XXXX21222^{\ 2222} + \epsilon$$

Where = response, β0 = overall coefficient (intercept), β1, β2 = Co-efficient of variables X1, X2 respectively, β12 = Co-efficient of interaction, β11, β22 = Co-efficient of quadratic terms,X1, X2 = independent variables.

Table 1: Independent Variables and Levels for 3^2 Full Factorial Design

Independent Variables	Low (-1)	Medium (0)	High (+1)
% PEG (X1)	12	17	22
% NaCl (X2)	5	10	15

Table 2: Dependent Variables for 3^2 Full Factorial Design

Response Variable	Description
Y1	% drug release at time 15 Min.
Y2	% drug release at time 540 Min.

Formulation of Experimental design batches

Experimental design batches were prepared as per 3^2 full factorial design. 9 batches were prepared as per design. The coded and decoded values of independent variables are given in Table 3.

Table 3: Coded and Decoded Values of Independent Variables for 3^2 Full FactorialDesign

Run	Formulation	Coded Value		Decoded Value	
		X1	X2	X1 (mg)	X2 (mg)
1	F-1	-1	-1	42	17.5
2	F-2	0	-1	59.5	17.5
3	F-3	1	-1	77	17.5
4	F-4	-1	0	42	35
5	F-5	0	0	59.5	35
6	F-6	1	0	77	35
7	F-7	-1	1	42	52.5
8	F-8	0	1	59.5	52.5
9	F-9	1	1	77	52.5

Design Batch Formulation Design Batch Formulation

Table 4: Design Batches Formulations (F1 - F9)

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	75	75	75	75	75	75	75	75	75
PEG 6000	42	59.5	77	42	59.5	77	42	59.5	77
NaCl	17.5	17.5	17.5	35	35	35	52.5	52.5	52.5
Stearic acid	215.5	198	180.5	198	180.5	163	180.5	163	145.5
Total Weight (mg)	350	350	350	350	350	350	350	350	350

Statistical Analysis of Design Batch

The experimental data obtained from all Formulations were validated using analysis ofvariance (ANOVA) and Regression analysis in Microsoft excel 2019. Design expert trial

version 13 was used to create Counter plots and response surface plots. Regression analysis using Microsoft Excel 2019 yielded a polynomial equation with useful terminology for the primary and interaction effects. The importance of the influence of variables on the answer in terms of their regression coefficient was discovered using this design optimization. ANOVA was used to determine the importance of factor influences on response regression coefficients.

(15)

Optimization of formulation

The trial version of the software Design Expert 13 was used to optimize the formulation of Extended-release moulded tablets.

Evaluation Parameters [16-21]Weight Variation

Twenty tablets will be chosen at random from each set and measured separately. Three batches'total weight and standard deviation (SD) will be calculated. It passes the weight deviation testif no more than two of the actual tablet weights deviate from the average weight by more thanthe permitted percentage deviance and no more than twice the percentage revealed. It is calculated with the help of an automated measuring balance.

Hardness

Monsanto hardness measuring instruments may be used to assess the hardness or crushing ability of the tablets. Three separate tablets from each batch will be checked, with the averagebeing the outcome.

Dimensions

Vernier callipers will be used to determine the dimensions of solid dispersion tablets. Ten different tablets from each batch will be used, with the average being the product.

Friability

Take 10 tablets weigh and add place them in Roche friability test apparatus at 25 RPM for 4 min. Weigh the tablets again and calculate the percentage friability. Weight loss of tablet should not be more than 1%. Friability = (initial weight of tablet – weight of tablet after test/initial weight of tablet) * 100

In-vitro Release

Drug release from moulded tablets is determined by using dissolution test United States Pharmacopoeia (USP) (0.1N HCl at 37ºC ± 2ºC in type II apparatus). At appropriate time intervals, 5 ml aliquots of dissolution media will be drained and replaced with fresh medium. Following withdrawal, samples are purified and processed using a suitable analytical procedureafter appropriate dilution. The concentration is measured using the normal calibration curve. Dosage form: Oral Tablet, Apparatus: USP type II apparatus (Paddle apparatus), Speed (RPM):50 RPM, Medium: 0.1 N HCl, Volume: 900 ml. [22-29]

RESULT AND DISCUSSION

In-vitro Release

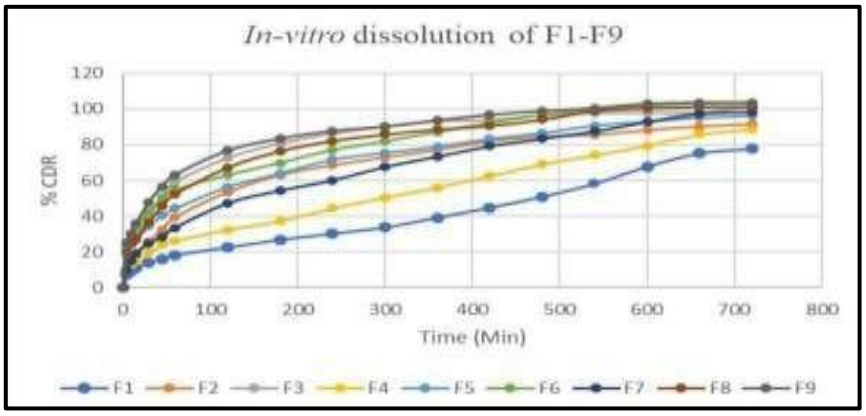
From the dissolution profile of design batches (F1-F9) we concluded that as the concentrationof HLB modifier (PEG 6000) and Channeling agent (NaCl) increase % drug release increases.

Table 5: Master In-Vitro Dissolution Profiles of All Design Batches F-1 to F-9 (% CDR)

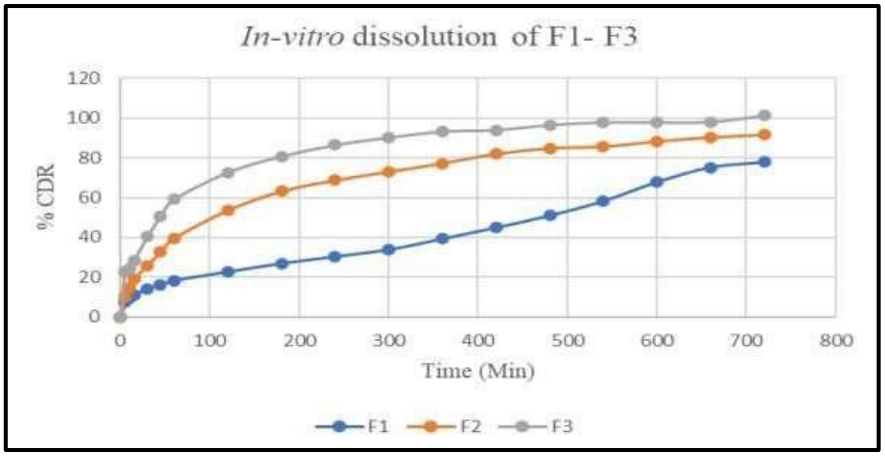
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	7.380	10.141	22.509	11.098	20.263	23.343	10.030	19.736	25.447

10	9.218	14.761	24.161	12.926	24.517	29.447	14.798	24.587	30.521
15	10.870	18.929	28.104	14.912	26.682	33.683	19.297	27.270	35.739
30	14.231	25.927	40.352	19.411	34.489	42.541	24.888	36.698	47.912
45	16.150	32.641	50.772	23.972	40.339	49.951	28.295	45.711	56.657
60	18.263	39.487	59.105	26.263	44.422	54.931	33.652	52.460	63.226
120	22.645	53.540	72.675	32.386	56.362	63.104	47.382	67.320	76.831
180	26.867	61.097	80.772	37.323	64.177	69.898	54.417	76.524	83.513
240	30.308	68.660	86.468	44.442	71.780	76.104	60.169	82.255	87.782
300	33.802	72.968	90.222	50.463	75.572	81.898	67.605	85.845	90.192
360	39.214	77.214	93.286	56.121	79.048	87.206	73.410	88.678	93.667
420	44.865	81.907	94.029	62.565	83.429	92.250	79.207	90.703	96.875

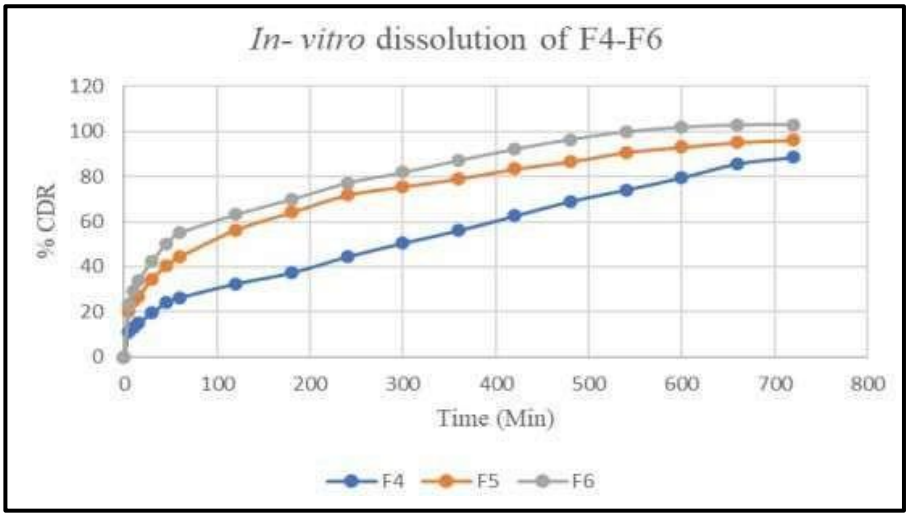
480	50.905	84.097	96.583	69.094	86.659	96.576	83.392	94.099	98.794
540	58.219	85.635	97.866	74.212	90.809	99.975	87.526	99.131	100.584
600	67.758	88.227	97.887	79.613	93.079	101.995	92.833	100.541	102.959
660	75.217	90.318	98.087	85.843	95.250	103.027	97.356	101.285	103.648
720	77.793	91.532	101.262	88.638	96.273	103.192	98.253	101.365	103.661

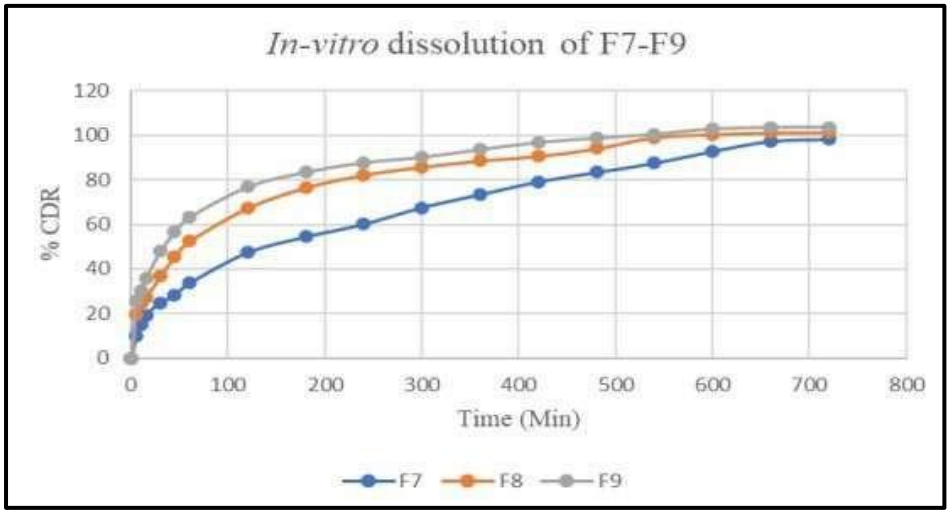


(a)



(b)





(d)

Figure 1: In-vitro dissolution profile of (a) F-1 to F-9, (b) F-1 to F-3, (c) F-4 to F-6,

(d) F-7 to F-9.

Generation of full model for selected 3^2 full factorial design

3^2 full factorial design was carried out with the 9 runs. Further, the evaluation of extended- release tablet of venlafaxine HCl was done and obtained responses were subjected for the regression analysis and relationship between the independent and dependent variable was findout with the help of full model equation. Hardness of F1- F9 batches found in range 2-3 Kg/cm^2 after which the tablet was found to change the shape significantly instead of breaking, while the friability of these batches found in range 0.386-0.521%.

Table 6: Data Transformation and Response Values of 3^2 Full Factorial Design

Run	Independent variable		Dependent variable	
	CodedValue	DecodedValue	Y1	Y2
	X1	X2	% CDR at 15 min	% CDR at 540 min
F1	-1	-1	10.870	58.219
F2	0	-1	18.929	85.635
F3	1	-1	28.104	97.866
F4	-1	0	14.912	74.212

F5	0	0	26.682	90.809
F6	1	0	35.683	99.975
F7	-1	1	19.297	87.526
F8	0	1	27.270	99.132
F9	1	1	35.739	101.584

Formulation of check point batchAccording to experimental design protocol, the optimized design batch (F-7) formulation wasprepared. Optimized Batch was evaluated for Weight variation, Diameter results are shown intable 7.

Table 7: Evaluation parameter of optimized batch

Weight Variation (mg)(n=3)	**Diameter (mm)(n=3)**
350.34 mg	17.76 mm

In-vitro drug release of optimized batch

In-vitro dissolution of optimized batch was carried out using paddle type II dissolution test apparatus (900 ml, 50 rpm, 37°C) in 0.1N HCl. Drug release profile is shown in Table 8 and figure 2.

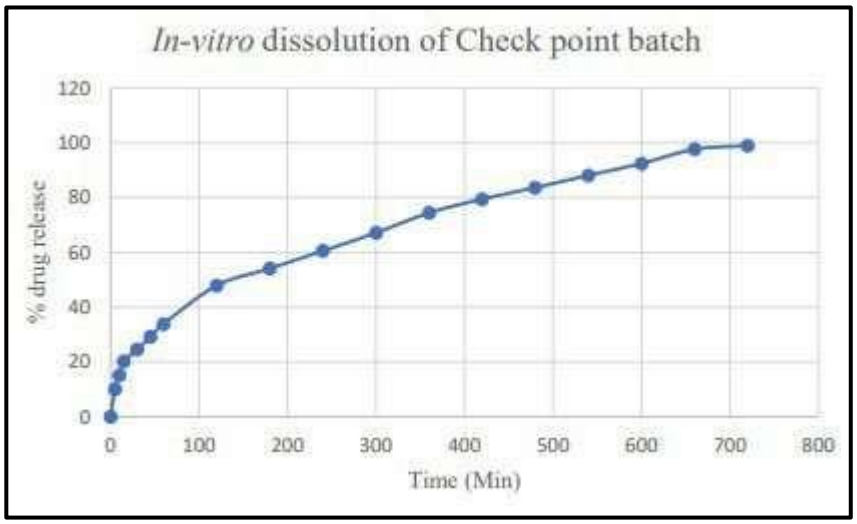


Figure 2: In-vitro dissolution profile of check point batch Table 8:

In-vitro dissolution profile of check point batch

Time (min)	**F7**
0	0.000
5	10.102
10	15.124
15	20.215
30	24.560
45	29.220
60	33.895
120	47.960
180	54.125
240	60.564

300	67.156
360	74.446
420	79.464
480	83.655
540	88.134
600	92.464
660	97.654
720	99.023

Comparison between experimental and predicted value of responses of Checkpoint batch
Observed value was found to be similar to the predicted values. Thus, it was confirmed that factors like % PEG and % NaCl are significant for the drug release from the formulation. Modelgenerated is thus, validated as shown in Table 9.
* [{(Predicted Value-Observed value)/Predicted value} *100]
Here, predicted and observed values are close to each other and % bias error is low. So, this design was validated.

Table 9: Result of check point batch

Response	**Observed Value**	**Predicted Value**	**% Bias Error***
% CDR at 15 Min.	20.215	20.599	1.86
% CDR at 540 Min.	88.134	90.021	2.14

Short term Accelerated Stability Study
It was performed at 45°C ± 2 and 75% RH for 1 month, after warping it in Aluminium foil andthen put it into desiccator. From the figure 3 concluded that there is not major changes found in the formulation after 1 month dissolution study[30-31].

Table 10:Stability study of optimized batch

Time (min)	**Optimized Batch % Drug Release**	**After 1 Month % Drug Release**
0	0.00	0.00
5	10.10	9.18
10	15.12	17.09
15	20.21	22.18
30	24.56	27.54
45	29.22	32.21
60	33.89	36.84
120	47.96	49.95
180	54.12	58.11
240	60.56	65.14
300	67.15	70.54
360	74.44	77.46
420	79.46	82.48
480	83.65	86.42
540	88.13	90.64
600	92.46	96.42
660	97.65	99.64
720	99.02	102.02
-	-	f1=4.90 f2 = 75.33

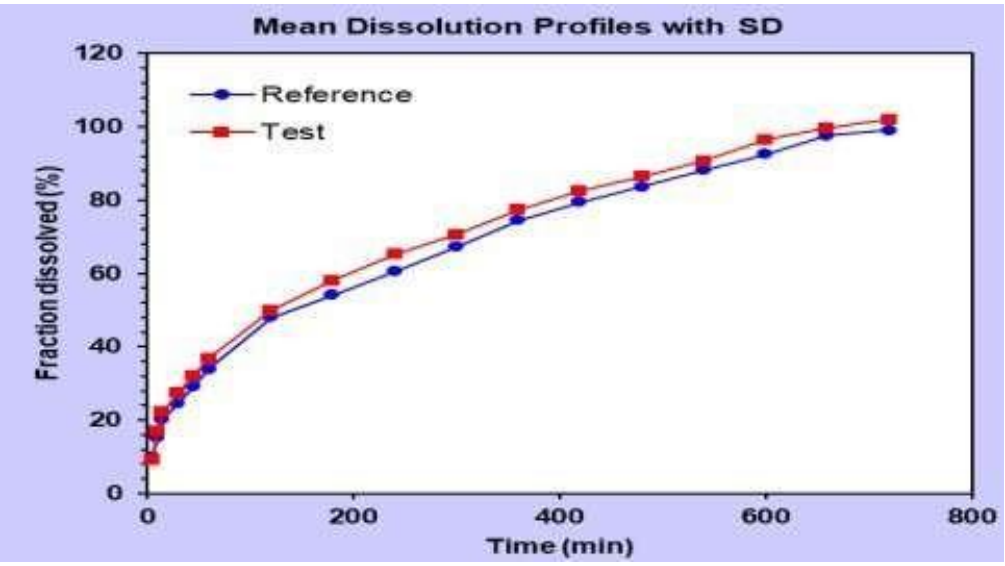


Figure 3: In-vitro % drug release profile of optimized batch after 1 month

CONCLUSION

The aim of this study was to prepare Extended-release Venlafaxine HCl tablet using Hot meltmoulded method. DSC, FTIR and analytical methods were used to identify drug. The Results showed that sample drug Venlafaxine HCl was pure in nature. Venlafaxine HCl is BCS Class I drug with high solubility high permeability. so difficult to prepare extended-release tablet butit was prepared by using hydrophobic base and hydrophilic base. preliminary trials revealed that an extended-release tablet of Venlafaxine HCl prepared with hydrophilic & hydrophobic base. NaCl was used as Channeling agent to increase the drug release by creating channel. From primary trial outcomes, it was concluded that two factors have significant effect on dissolution of Venlafaxine HCl. One was % PEG and other was % NaCl. 3^2 full factorial design was applied to optimize formulation. Where % PEG (X1) and % NaCl were taken as independent variable and % drug release at 15 min and % drug release at 540 min was taken as response variable. The formulation of design batches was evaluated for hardness, weight variation, diameter, dissolution study. Optimized batch was derived statically using desirabilityfunction. The model was validated by formulating the check point batch. Optimized batch (F-7) showed drug release 19.297% at 15 min and drug release 87.526 % at 540 min which was desired for extended-release tablet of venlafaxine HCl. Check point batch was prepared as perthe desired criteria and compared between predicted and experimental responses. The result...revealed that there was no significant difference between predicted and experimental responses. As a result, design was validated. Short term stability study of optimized batch wascarried out and evaluated with dissolution study from this 75.33 similarity (f2) found. The present study thus explores that hot melt method has promising approach for drug having highsolubility & high permeability

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