

# Optimization and evaluation of Venlafaxine Hydrochloride fast-dissolving oral films

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## Abstract

Three factors, three level full factorial design was used to develop venlafaxine HCl fast dissolving oral films (FDOFs) to optimize the concentrations of the film forming polymer; hydroxypropyl methylcellulose HPMC (X1), super disintegrant; sodium starch glycolate SSG, (X2) and glycerol as the film plasticizer (X3). Effects of the three factors on the disintegration time (Y1), swelling index (Y2), and dissolution efficiency at 15 min; DE%15 (Y3) of the prepared FDOFs were evaluated by using statistical models. The optimized film formula was characterized in term of x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and morphological characteristics. Disintegration time was found to increase with the increase in HPMC (X1) concentration, and the shortest disintegration time ( $21.67 \pm 2.08$  s) was observed in case of F2 formula (lowest HPMC level and highest glycerol level in absence of SSG). The highest swelling index ( $3.64 \pm 0.59$ ) was observed in case of film formula F1 (medium concentrations of both HPMC and glycerol and highest SSG concentration). The results also indicated that as the concentration of HPMC increased the DE%15 decreased. SSG (X2), with highest value ( $72.33 \pm 1.71\%$ ) was recorded for in case of F12 (using 2% HPMC, 5%SSG and 1.5% glycerol). The optimized FDOF formula derived by the statistical models suggested 2% HPMC, 5% SSG, and 1% glycerol. The data obtained from DSC and XRPD revealed no interaction between drug and FDOT excipients. In addition, XRPD studies proved that the venlafaxine HCl was homogeneously dispersed in the film matrix.

**Keywords:** Fast Dissolving, Oral films, HPMC, FDOT, Venlafaxine Hydrochloride.

## 1. Introduction

Drug delivery technologies adjust drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance [1-2]. Oral route of administration is considered as the most common route for drug systemic actions owing to its flexibility, ease of use and painlessness, as well as patient compliance [3-4].

Fast dissolving films are the most advanced solid dosage form in term of their flexibility. The formulation of fast dissolving buccal film is composed of material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agents, flavoring agents, coloring agents, surfactant, permeation enhancers, and super disintegrants [5-7]. These dosage forms are beneficial in patients such as pediatric, geriatrics, bedridden, emetic patients, diarrhea, sudden episode of

allergic attacks, or coughing for those who have an active life style [8]. Administration of oral disintegrating dosage forms offers additional advantage for treatment of patients with psychiatric disorders. The delivery system consists of a very thin oral strip, which is placed on the patient's tongue or any oral mucosal tissue [9]. The strip is instantly wet by saliva and the film rapidly hydrates and disintegrates and dissolves to release the medication for or mucosal absorption, or with formula modifications, will maintain the quick-dissolving aspects that allow for gastrointestinal absorption to be achieved when swallowed [10-11].

Also, FDOFs are targeted for mentally ill patients, the develop mentally disabled patients, and patients who are uncooperative. FDOFs are also useful when local action is desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething [12-13]. Venlafaxine hydrochloride is a structurally antidepressant for oral administration.

It is designated 1-[2-(dimethylamino) 1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride or ( $\pm$ )-1-[a-[(dimethyl-amino)methyl]-p-methoxybenzyl] cyclohexanol hydrochloride. Venlafaxine hydrochloride solubility in water is 572 mg/mL [14]. Venlafaxine HCl is an antidepressant of the serotonin-norepinephrine reuptake inhibitor (SNRI) class. Psychotic patients may spit out oral medication because of its undesirable taste or find injectable dosage form unacceptable or contraindicated [15]. In addition, psychotic patient is agitated or shows difficulty in swallowing. Administration of oral disintegrating dosage forms offers additional advantage for treatment of patients with psychiatric disorders [16]. Remeron Sol Tab orally disintegrating tablets of the antidepressant drug, mir tazapine showed a positive opinion among the patients about the taste of medication, showed that formulations of antidepressant drugs as oral disintegrating dosage forms can offer convenient alternatives to traditional tablets and may support patient compliance with extended therapy [17]. Several investigators showed that formulations of venlafaxine HCl as oral disintegrating tablets can offer convenient alternatives to traditional tablets and may support patient compliance with extended therapy. Formulation of venlafaxine hydrochloride as FDOFs is probable to result in rapid absorption with fast onset of action, and can also improve its bioavailability and help partial evading its first pass effect [18]. In addition, patient compliance and adherence can be improved when the drug is formulated as FDOF due to masking its undesirable taste. The aim of this study was to formulate and optimize FDOFs containing venlafaxine HCl using 33 full factorial designs, in addition to study the influences of formulation parameters on the film attributes (disintegration, swelling index, and dissolution efficiency; DE %15) [19-20].

## 2. Materials and Methods

Venlafaxine Hydrochloride (Drug) powder was obtained from Zydus pharmaceuticals. And other Excipients like HPMC, PVP K30, PVA, Xanthan gum, Guar gum, PG, Glycerin, PEG 400, Mannitol, Citric acid and Tween 80 were obtained from ACS chemicals

### 2.1 Formulation and preparation

Oral films were prepared by using solvent casting technique. The required amount of film forming polymer was allowed to hydrate in a minimum amount of distilled water for one-two hours. Then it uniformly dispersed to get clear viscous solution of film forming polymer. Then after the required quantity of plasticizer was added to polymer solution (Solution A). All other ingredients including drug were dissolved in another beaker in minimum amount of water (Solution B). Solution B is added into solution A with

constant stirring to form clear viscous aqueous solution containing homogeneously dispersed drug (Solution C). The above produced solution was set aside in uninterrupted condition until entrapped air bubbles were removed. The aqueous solution was casted in Petri dish made up of glass (62.17cm<sup>2</sup>)

Dose calculation of Venlafaxine Hydrochloride

Oral dose of Venlafaxine hydrochloride is 25 mg

Each film contains 25 mg

of Venlafaxine hydrochloride

Area of each film =  $2*2 = 4$  cm<sup>2</sup>

Area of Petri dish =  $\pi r^2$  (where r = Radius of Petri dish) =  $3.14*(4.45)^2 = 62.17$  cm<sup>2</sup> 4 cm<sup>2</sup>

area of film contains 25mg Venlafaxine hydrochloride 62.17cm<sup>2</sup>

area of film contains =  $62.17*25/4 = 388.562 \sim 389$  mg

Venlafaxine hydrochloride was taken for whole petri plate area

### 2.2 Evaluation of oral film:

#### 2.2.1. Film thickness:

##### Sample Preparation

Proper preparation ensures accurate measurement and prevents artifacts in the image.

a. Cutting the Film: Use a sharp scalpel, microtome, or razor blade to cut a small piece (~5 mm  $\times$  5 mm). Cut the film perpendicularly to its plane to expose a clean cross-section. Optionally, freeze fracture the film in liquid nitrogen for brittle, clean break.

b. Mounting: Mount the film vertically or cross-sectionally on a standard SEM stub using Double-sided carbon tape, or Conductive adhesive. Ensure the cross-sectional surface is exposed to the electron beam. Use tweezers and antistatic tools to avoid contamination or damage.

c. Sputter Coating (if required): Most films (especially oral or polymeric) are non-conductive and require coating to avoid charging. Apply a thin conductive layer (5–20 nm) using a sputter coater with Gold (Au), Platinum (Pt), Carbon (C). Ensure uniform coating to improve image clarity and prevent artifacts.

**FILM pH:** Three films of each formulation were dissolved in beaker containing 5 ml of distilled water. The solution was measured by PH meter. A mean of three readings and standard deviation was recorded.

#### 2.2.2 Film Moisture Content

Moisture content tests were performed to ensure dryness. The prepared films were initially weighed and located in the desiccators containing calcium chloride. After 3 days the films were reweighed to obtain the percentage of moisture loss. Three films of each formula were used in this test.

$$\% \text{ Moisture content} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} * 100$$

**Table 1: Moisture Content**

S. No.	Formulation	Moisture content
1	F1	4.64
2	F2	0.66
3	F3	2.42

**2.2.3 Drug Content:**

Venlafaxine HCl-loaded FDOF was placed in 100 ml volumetric flask, then dissolved in 50 ml phosphate buffer (pH 6.8) using magnetic stirrer. The volume was completed with phosphate buffer (pH6.8). One ml of the solution was further diluted to 10 ml with phosphate buffer solution (pH 6.8) and the absorbance was measured at 225 nm using UV spectrophotometer against a suitable blank prepared from non-medicated film. Drug content uniformity was conducted in triplicate. The films were accepted in terms of drug content when the range for drug content is between 85 and 115%. A mean of three readings and standard deviation was recorded. Three films of each formula were used in this test.

**2.2.4 Swelling index**

The studies of swelling index of the film were conducted in 6.8 pH phosphate buffer solution. A film was weighed and placed in a pre-weighed stainless steel wire sieve. The mesh containing the film was submerged into 15 ml of phosphate buffer 6.8 pH contained in a petri dish. The increase in film weight was determined at each interval (1 min) until a constant weight was observed. Three films of each formula were used in this test. The degree of swelling was calculated using the formula:

$$SI = (W_t - W_0) / W_0$$

where SI = swelling index

W<sub>t</sub> = weight of the film at time "t"

W<sub>0</sub> = weight of the film at t = 0

**2.2.5 In-vitro disintegration:**

Disintegration of venlafaxine HCl-loaded FDOFs was performed using disintegration tester. Three films of each formula were tested. One film of each formula was placed in one of the six tubes of the basket. Then the apparatus was operated using phosphate buffer pH 6.8 as disintegration medium and maintained at 37°C±2°C. The disintegration time was recorded.

**2.2.6 In-vitro dissolution:**

*In-vitro* dissolution test of venlafaxine HCl-loaded oral films was performed using USP dissolution apparatus (Type II). The test was carried out at 37°C ± 0.5°C with stirring speed of 100 rpm in 900 ml of phosphate buffer (pH 6.8). Samples were withdrawn at predetermined time intervals (2, 5, 10, 15, 20, 30 45 and 60 min) and replaced with the same volume of fresh buffer, in which sink conditions were maintained during dissolution. The absorbance was determined at 225 nm using UV-visible spectrophotometer against a blank made of non-medicated

films at the same conditions. The amount dissolved from each film was calculated. Three films of each formula were tested.

**2.2.7 Differential Scanning Calorimetry (DSC):**

The DSC scans were recorded for venlafaxine HCl FDOFs compared to that of the individual components and physical mixture, to determine any physical or chemical interaction between the drug and the excipients used in the preparation of FDOFs. The samples (3–5 mg) were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min, over a temperature range of 25–350°C. Thermo grams of the samples were obtained using differential scanning calorimetry. Thermal analysis data was recorded using a TA 50I PC system with Shimadzu software programs. To calibrate the DSC temperature and enthalpy scale, indium was used as a standard. Nitrogen gas was used as purging gas at rate of 40 ml/min. The samples that were used were venlafaxine HCl, HPMC, SSG, saccharine sodium, citric acid, and optimized FDOF.

**2.2.8 Melting point:** The melting point of drug was found out by capillary method and measured value was compared with the literature survey.

**2.2.9 Determination of  $\lambda$  max:** Solution of Venlafaxine hydrochloride (10 $\mu$ g/ml) was prepared in the stimulated saliva (pH 6.8) and the solution was scanned for absorbance between 200–400 nm using UV spectrophotometer. 221 nm in Stimulated Saliva pH 6.8. The  $\lambda$ max is the wavelength at which a substance shows **maximum absorbance** in the UV-Visible range (typically 200–800 nm). Measuring at  $\lambda$ max ensures the **highest sensitivity and accuracy** for drug quantification.

**2.2.10 Physical characterization by FTIR:** The IR studies were carried out by Fourier Transform Infra-red (FTIR) instruments. Identify **characteristic peaks** of the drug (e.g., –OH, –NH, C=O, C=C, etc.). Check for **peak shifting, broadening, or disappearance** indicating **Drug-polymer interaction, Hydrogen bonding, Compatibility or incompatibility**, confirm that the drug remains chemically stable and unchanged during formulation. Venlafaxine hydrochloride was mixed with combination of polymers in ratio of 1:1 and kept in FT-IR (Shimadzu Miracle 10). Venlafaxine hydrochloride along with other excipients.

### 3. Result and discussion

#### 3.1 Pre-formulation Studies:

**FILM Ph:** A mean of three readings and standard deviation was recorded.

**Table No. 2: Result of pH**

S. no.	Formulation	Mean Ph ± SD
1	F1	4.26±0.04
2	F2	2.90±0.02
3	F3	4.20±0.11

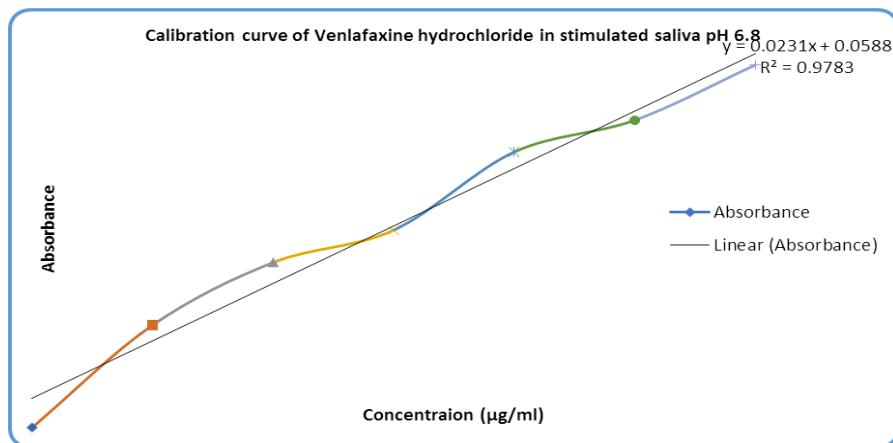
### 3.2 FTIR Interpretation Data of Drug and Polymers:

**Table No. 3: Result of FTIR Of Drug and Polymers**

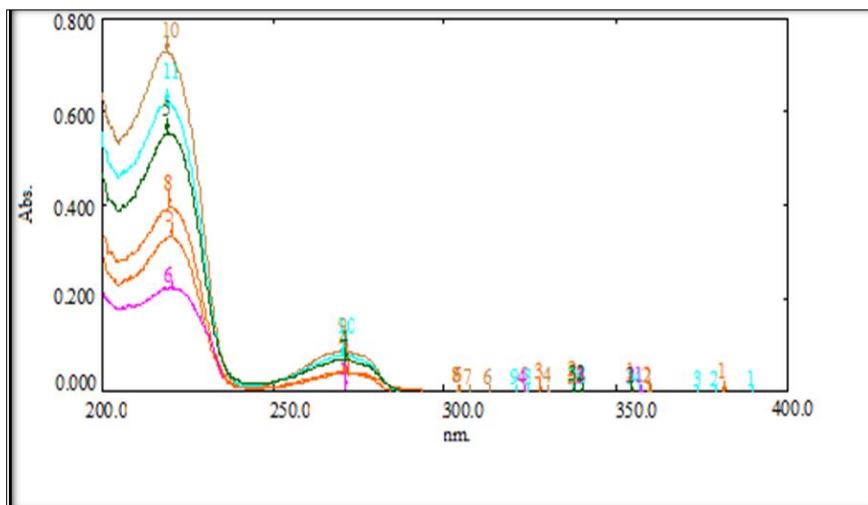
Sr. No	Functional group	Standard value	Observed value (Drug)	Observed value (Drug+Excipient)
1	OH	3650-3584	3601.10	3684.04
2	CH stretching	1480-1380	1433.11	1423.47
3	C <sub>6</sub> H <sub>5</sub>	1500-1600	1510.26	1512.19

**Table 4: U.V. Spectrophotometer readings of Venlafaxine Hydrochloride at 221 nm. (STD at 224nm)**

Concentration ( $\mu$ g/ml)	Absorbance at 221nm			Mean Absorbance $\pm$ SD (n=3)
0	0	0	0	0
5	0.206	0.209	0.215	0.210 $\pm$ 0.004
10	0.332	0.319	0.337	0.329 $\pm$ 0.009
15	0.397	0.389	0.412	0.399 $\pm$ 0.011
20	0.554	0.547	0.560	0.553 $\pm$ 0.006
25	0.618	0.611	0.645	0.624 $\pm$ 0.017
30	0.729	0.719	0.724	0.724 $\pm$ 0.005



**Figure 1: Calibration curve of Venlafaxine Hydrochloride**



**Figure 2: Overlay Spectrum for various concentration of Venlafaxine Hydrochloride Factorial Design Was Applied to Optimized Batch**

**Table 5: Formulation of factorial batches F1 to F4.**

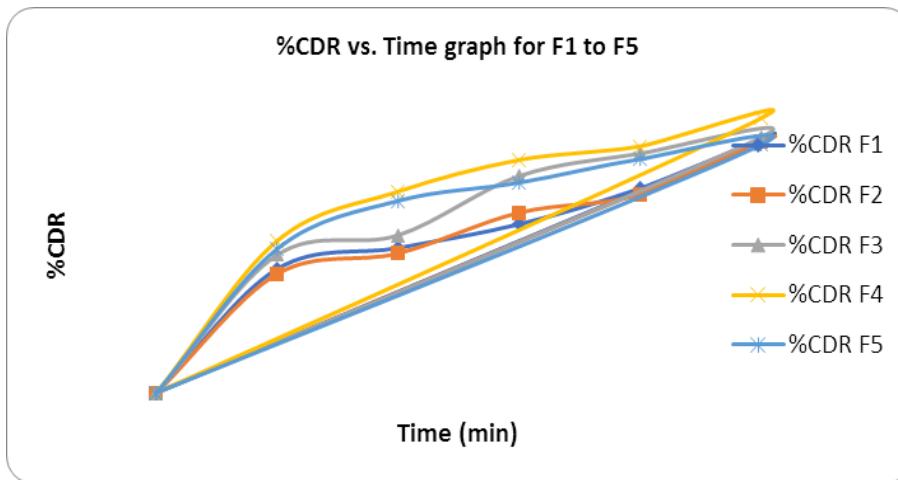
Ingredients (mg)	F1	F2	F3	F4
<b>Venlafaxine hydrochloride</b>	25	25	25	25
<b>HPMCE15</b>	14	16	18	14
<b>PVA</b>	2	2	2	4
<b>Propylene glycol</b>	4	4	4	4
<b>Mannitol</b>	2.4	2.4	2.4	2.4
<b>Citric acid</b>	2.4	2.4	2.4	2.4
<b>Tween80</b>	q.s	q.s	q.s	q.s
<b>Water</b>	q.s	q.s	q.s	q.s

**Table 6: Evaluation Parameters for F1 to F4**

Evaluation Parameters	Factorial Batches			
	F1	F2	F3	F4
Appearance	Good	Moderate	Good	Good
Separability	++	+	++	++
Folding Endurance	171	203	180	265
Mechanical Properties				
Tensile Strength (gm/cm <sup>2</sup> )*	9.41±0.57	10.65±1.22	12.09±0.33	10.12±0.48
%Elongation	10	10	15	15
Thickness(mm)*	0.073±0.011	0.086±0.005	0.09±0.01	0.096±0.005
Surface pH	6.27	6.48	5.95	6.52
Disintegration Time(sec)*	11.66±0.57	20.33±0.57	30.33±0.57	14.66±1.52
Assay (%)	86.43	81.39	91.65	94.26

**Table 7: In Vitro drug release for F1 to F4.**

Time (min)	% CDR			
	F1	F2	F3	F4
0	0	0	0	0
1	41.94±0.64	40.23±0.91	46.65±0.64	51.40±0.51
2	48.99±0.46	47.17±0.75	53.28±0.60	68.03±0.45
3	57.03±0.44	60.91±0.65	73.26±0.63	78.69±0.70
4	69.10±0.62	67.02±0.25	80.83±0.31	84.38±0.57
5	85.63±0.39	84.95±0.54	86.33±0.44	92.78±0.75

**Figure 3: % CDR for batches F1 to F5.**

#### 4. Discussion

Factorial batch F1 produced films having good appearance and were having good separability but tensile strength value was less as compared to other and drug release profile was not desirable. F2 batch produced film with moderate appearance. Factorial batch F3 produced film having good appearance, having somewhat higher disintegration time as compared to F4 batch. tensile strength but disintegration time was somewhat higher as compared to F4. However, but it has higher disintegration time as compared to all other batches because of higher polymer content. Factorial batch F4 has given less disintegration time. Also, it has desirable mechanical

properties that are comparatively moderate tensile strength and having desirable % elongation that means soft and tough film formulated. Thus, F4 considered as an optimized batch. Also, it releases the drug in a desirable manner.

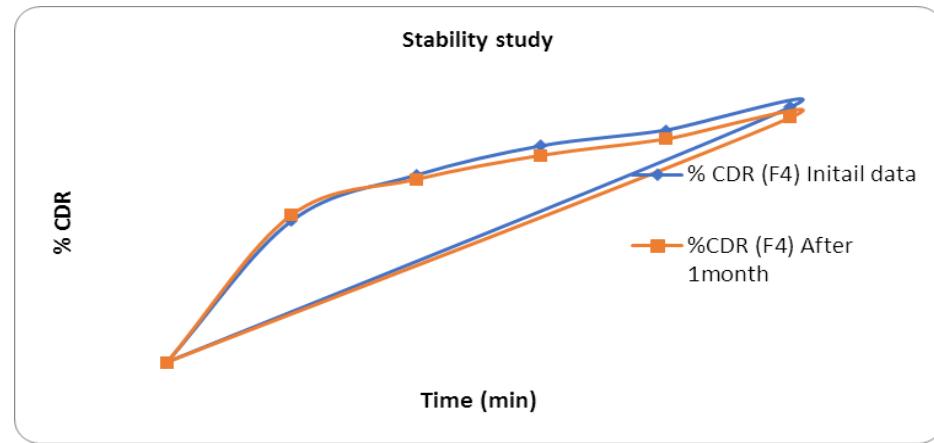
**4.1 Stability Study:** Stability studies were done according to ICH guidelines. The stability studies were carried out on the optimized satisfactory formulations as per ICH guidelines. The optimized formulation after factorial design batch F4 was sealed in aluminum foil packaging and kept in humidity chamber at fixed temperature and humidity. Here stability study was carried out in accelerated conditions at  $40 \pm 2$  °C and  $75 \pm 5\%$  RH for 1 month.

**Table 8: Evaluation after one month.**

Evaluation parameters	Batch F4	
	Initial Data	After 1 month
Appearance	Good	Good
Separability	++	-
Folding Endurance	260	249
Mechanical Properties		
Tensile Strength(gm/cm <sup>2</sup> )	10.12	9.58
%Elongation	15	15
Thickness(mm)	0.096	0.10
Surface pH	6.52	6.49
Disintegration Time(sec)	14.66	15
Assay (%)	94.26	93.69

**Table 9: In vitro drug release before and after.**

Time (min)	%CDR (F4 Batch)	
	Initial Data	After 1 month
0	0	0
1	51.40	53.56
2	68.03	66.51
3	78.69	75.23
4	84.38	81.12
5	92.78	89.98



**Figure 4: %CDR vs. Time Graph for Batch of stability study.**

The above stability data at 40°C/75 % RH, shows that there was no significant difference in % CDR of the formulation F4 before and after a month results. This concluded that the optimized formulation has sufficient stability at 40°C and 75% RH and extrapolated that the formulation was stable at room temperature. So, the formulation after one month was found to be stable.

## 5. Summary and conclusion

According to various batches formulated, it was concluded that amongst Preliminary batches B1 to B5 (plasticizer and its concentration) batch B4 containing PG was optimized as plasticizer as it produced clear and smooth film with good elasticity and folding endurance. Factorial batch F4 was concluded as optimized batch by taken in consideration of different evaluation parameters which have desired properties. Factorial batch F4 had contained HPMC E15 and PVA in 14mg and 4mg quantity respectively in a combination. Optimized batch F4 was kept for stability study for a month and readings were taken after one month. The optimized batch produced the film containing drug Venlafaxine hydrochloride was having desired disintegration time and mechanical properties that is potentially useful for the treatment of depression where faster onset of action is required.

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