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**Mangesh R Bhalekar**
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, Maharashtra, India

**Ashwini R Madgulkar**
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, Maharashtra, India

**Sumedha S Andure**
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, Maharashtra, India

**Correspondence**
**Mangesh R Bhalekar**
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, Maharashtra, India

# Formulation and evaluation of sustained release pellets of venlafaxine hydrochloride

**Mangesh R Bhalekar, Ashwini R Madgulkar and Sumedha S Andure**

**Abstract**
The objective of this study was to formulate, optimize and evaluate sustained release pellets of venlafaxine hydrochloride. Venlafaxine hydrochloride sustained release pellets were prepared by solution layering technique. The effect of polymer (Eudragit RLPO) and binder polyvinyl pyrolidone (PVP-K30) on the % drug content and % drug release after 12$^{th}$ hour was optimized by using $3^2$factorial design. It was observed that concentration of polymer directly affects the drug release profile and concentration of binder affects the % drug content. The effect of the variables and behavior of the system was studied using response surface plots. Non-pareils were coated by drug solution in a pan coater. Drug loaded pellets were coated dispersion of Eudragit RLPO and triethyl citrate. Tri-ethyl citrate was used as plasticizer. Pellets were evaluated for flow properties, drug content, *in-vitro* release characteristics, %coating efficiency, surface morphology, FTIR, differential scanning calorimetry. The release of optimized formulation batch was compared with marketed product (VENLOR-XR) and that was found to be similar.

**Keywords:** Venlafaxine hydrochloride, eudragit RLPO, Polyvinyl pyrolidone, solution layering technique, pellets

## 1. Introduction
Pellets are spherically shaped particles of 0.5 to 2.0 mm in diameter. They have many advantages over single unit dosage forms because they disperse freely in gastrointestinal tract, thus maximizing bioavailability and minimizing inter and intra individual variability in plasma level of drug.[1] Moreover, pellets containing incompatible active ingredient and/or different release profile can be blended together to be delivered simultaneously. They can be also divided in several strengths without making formulation and process change. Solution and suspension layering are some most frequently used techniques for production of pellets in industry. Goal of any pellet layering process is to achieve increase in diameter of starter pellets without the change in the number of units in a batch and therefore formulation of film coating liquid and parameters of coating process have to be adjusted to avoid agglomeration of pellets during layering. Both solution and suspension layering techniques require presence of binder in formulation for obtaining coherent layer. Binder level is determined experimentally so as to obtain good adhesion and minimize loss of active ingredient. [1]
The oral route of administration of drugs is the most important method for achieving systemic effects. In the process of absorption of drug from oral route, dissolution is the rate limiting step. Venlafaxine is an antidepressant, having elimination half life 5±2 hours and its maximum daily dose is 300 mg, making it an ideal candidate for extended release formulation. Since the drug belongs to BCS class-I, it is more hydrophilic in nature and suffers disadvantage of extensive hepatic first pass metabolism. [3]
Various methods to sustain the drug release of venlafaxine have been reported in literature using ion exchange resin [3], multiunit pellet system using HPMC polymer [13], coated pellets using eudragit polymer. [2]
Eudragit RLPO is highly permeable and permeates the drug independent of pH of digestive tract. Hence it was a choice of polymer for pellets formulation. [2]
The objective of the study was to prepare Venlafaxine hydrochloride pellets by solution layering technique, coating them with the sustaining release polymer Eudragit RLPO using pan coater to meet desired dissolution pattern. The formula was optimized by a $3^2$ factorial design optimizing concentrations of binder (PVP) and coating polymer (Eudragit RLPO).

## 2. Material and Method

### 2.1 Materials

Venlafaxine hydrochloride (VH) was received from Lupin pharmaceuticals as gift sample. Eudragit RLPO (Evonik industries, Mumbai), Non-pareil seed of MCC (ACG worldwide Mumbai), Triethyl citrate (Cosmo Chem, Pune), Poly vinyl pyrrolidone k-30 (ANALAB chemicals, Mumbai), Talc (ANALAB chemicals, Mumbai) and Potassium dihydrogen orthophosphate (S.D. Chem. Ltd, India). All other chemicals and reagents were of analytical grade.

### 2.2 Methods

#### 2.2.1 Drug Excipient Compatibility Studies

Compatibility of venlafaxine hydrochloride with polymer Eudragit RLPO and PVP K-30 in 1:1 ratio of physical mixtures were analyzed by Fourier transform- infrared spectroscopic analysis (FT-IR) and differential scanning calorimetry method.

#### 2.2.2 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform infrared spectrophotometer. The analysis was carried out in Shimadzu-IR Spectrophotometer. Samples were dispersed in KBr and compressed into pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 4000-400 $cm^{-1}$ and resolution was $1cm^{-1}$.

#### 2.2.3 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) studies were carried out using DSC *e software. Samples were accurately weighed and heated in sealed aluminium pans at a rate 10°C/min between 25- 350°C temperature range under nitrogen atmosphere. Empty aluminium pan was used as a reference.

#### 2.2.4 Preparation of coated pellets [4]

Venlafaxine hydrochloride loaded pellets were prepared by layering a drug-binder solution onto non-pareil beads using pan coater (R&D coater INSTACOAT, IC Deluxe, Mumbai). First, Venlafaxine hydrochloride (3.4 g) was dissolved in water (20 ml) and PVP K-30 (0.15 g, 0.30 g, 0.45 g) was mixed with water separately, both the solutions were mixed and sprayed onto non-pareil beads using pan coater. The layered pellets were dried at 40°C to evaporate residual water. The composition of drug coating solution mentioned in Table no 1.

#### 2.2.5Polymer coating on drug layered pellets [8]

Eudragit RLPO was dissolved in sufficient quantity of water and sonicated for 20 minutes then this polymeric solution was plasticized with 10% triethyl citrate. Drug layered pellets coated with the polymeric solution at a rate of 1 ml/min. The composition of polymer coating solution mentioned in Table no 2 and the process parameters are listed in Table no.3

**Table 1:** Composition of drug coating solution for Venlafaxine hydrochloride

| Sr. No | Ingredient | Quantity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | Venlafaxine hydrochloride (g) | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 | 3.4 |
| 2 | PVP K-30 (g) | 0.15 | 0.30 | 0.45 | 0.15 | 0.30 | 0.45 | 0.15 | 0.30 | 0.45 |
| 3 | Distilled water (ml) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

**Table 2:** Composition of polymer coating solution

| Sr. No | Ingredients | Quantity | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| 1 | Eudragit RLPO (g) | 1.5 | 3.0 | 4.5 | 1.5 | 3.0 | 4.5 | 1.5 | 3.0 | 4.5 |
| 2 | Tri-ethyl citrate (ml) | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| 3 | Talc (g) | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 | 2.0 |
| 4 | Distilled water (ml) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

**Table 3:** The process parameters used for coating drug and polymer

| Parameters | Venlafaxine hydrochloride layering | Sustained release polymer coating |
|---|---|---|
| Inlet temperature(°C) | 45-50 | 35-40 |
| Outlet temperature(°C) | 30-40 | 27-30 |
| Bed temperature(°C) | 34-37 | 30-32 |
| Nozzle diameter(mm) | 1 | 1 |
| Spray rate(ml/min) | 1 | 1 |
| Atomization pressure(bar) | 2.0 | 2.0 |

#### 2.2.6 % coating efficiency: [1]

The % coating efficiency was calculated by using the formula: $\%\ \text{Coating efficiency} = \frac{a-b}{c} \times 100$

Where,

a= Final weight of coated pellets in grams; b= Initial weight of pellets (Blank pellets in grams); c= Total amount of coating material (grams).

## 3. Experimental design and statistical analysis

In this study, a $3^2$ full factorial design was employed to optimize the formulation of pellets. In order to optimize formulations, the amount of Eudragit RLPO and the amount of PVP K-30, were chosen as independent variables. Eudragit RLPO being hydrophilic is more permeable to water so it sustained the release of drug. PVP k-30 is also hydrophilic and acts as a binder and viscosity enhancer. Hence the combination of a release sustaining and binder was used to obtain sustained release of drug. Selection of

response variables was crucial. The target was to obtain the drug release for 12 hours. Therefore the response variables selected for evaluation of sustained release were percent drug content and percent drug release at 12th hour was selected as dependent variables.

### 3.1 Analysis of data

The data obtained by experimental design was processed using Design expert 10.0 software. 3-D response surfaces curves were constructed to study the effect of two independent variables alone and in combination on % drug release at 12th hour and % drug content. All the responses, observed were simultaneously fitted to quadratic models and were evaluated in terms of statistical parameters. (Table no.4) Grid search was conducted over the experimental domain to find the compositions of the optimized formulations. The resultant experimental values of the responses were quantitatively compared with that of the predicted values by calculating residual and linear plots.

**Table 4:** Independent variables and their selected levels for pellet formulation

| Coded factor | Level | Factor 1 Conc. of Eudragit RLPO | Factor 2 Conc. of PVP K-30 |
|---|---|---|---|
| -1 | Low | 1.5 | 0.15 |
| 0 | Medium | 3.0 | 0.30 |
| +1 | High | 4.5 | 0.45 |

## 4. Evaluation of pellets

### 4.1 Flow properties of pellets

The flow properties of coated pellets like angle of repose, bulk density tapped density, carr's index, housner's ratio, etc were determined as mentioned in literature.[15,16]

### 4.2 Determination of % drug content

To determine percent content of venlafaxine hydrochloride in the pellets, accurately weighed crushed pellets (50 mg) were dissolved in 50 ml methanol, solution was filtered and analyzed spectrophotometrically at 226 nm after suitable dilution.

### 4.3 *In-vitro* drug release: [11]

USP dissolution apparatus, type I (LAB INDIA DS 8000) was employed to study the percentage of drug release from various formulations prepared. Capsule containing accurately weighed quantities of drug loaded pellets equivalent to 37.5 mg of venlafaxine hydrochloride of each batch were taken in 900 ml dissolution medium and drug release was studied at 100 rpm and at a temperature of 37±0.5 °C. 5 ml of dissolution medium was withdrawn periodically at regular interval of 1 hour and was replaced with the same volume of fresh medium. The withdrawn sample were filtered through whattmann filter and analyzed spectrophotometrically at 226 nm for drug release. As well as marketed formulation was analyzed.

### 4.4 Similarity factor

Similarity factor value was calculated for marketed formulation Venlor-XR and developed optimized batch using the formula,

$F_2$= 50log {[1+/N) Σ (Ri-Ti) $_2$-0.5X100}

Where N is the number of time points, Ri and Ti are dissolution of reference and test products at time I respectively. $F_2$ values greater than 50 considered as two products are similar and showed similar drug release profile. [13]

### 4.5 Drug release mechanism: [14]

Drug release data were analyzed by various mathematical models. Five kinetic models including zero order, first order, Higuchi, Peppas, Hixon-crowell release equations were applied to process the *in-vitro* release data. The equations are shown in Table 5, where Qt is the drug released fraction at time t, ko is the zero order release rate constant, k1 is the first order release rate constant and kH is the Higuchi release rate constant, t is the release time, n is the parameter that depends on the release mechanism and the shape of the matrix tested. The optimum values for the parameters present in each equation were determined by linear or non-linear least-squares fitting methods.

**Table 5:** Equations for drug release data analysis

| Model name | Equation |
|---|---|
| Zero order model | $Qt = K_0t$ |
| First order model | $In(Q_0-Q_{t)=} .k_1t+ InQ_0$ |
| Higuchi-diffusion model | $Q_t= k_Ht^{1/2}$ |
| Kosmeyer - peppas model | $In\ Q_t = n\ Int+k$ |

### 4.6 SEM studies

The surface morphology of pellets was determined by scanning electron microscopy (SEM). Photographs were taken and recorded at suitable magnification. (Instrument: FEI, Model: Nova nano SEM 450).

## 5. Result and Discussion

Eudragit polymer is primarily used in film coating in tablet and capsule dosage forms. Films of different grades can be produced by using different polymer grades. Eudragit RLPO is highly permeable and allows drug permeation across the film independent of pH of digestive tract. Hence it is a polymer of choice for pellets formulation.

### 5.1 Fourier Transform Infrared spectroscopy

To study the compatibility of the drug with excipient IR spectra of the drug in combination with excipient in 1:10 ratio was studied. The IR spectrum shown in fig 1 indicates that there was no physicochemical interaction in between drug and the used excipient. The spectra obtained FTIR spectroscopy studied at wavelength 4000-400cm$^{-1}$.

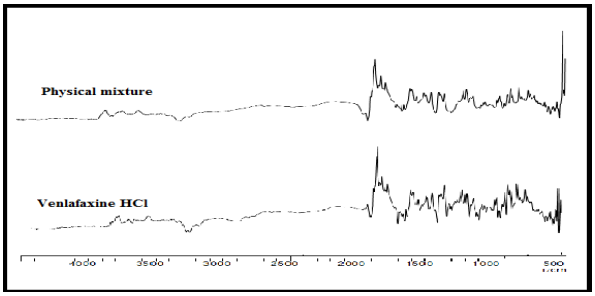


**Fig 1:** FTIR spectrum of Venlafaxine hydrochloride and physical mixture.

**Table 6:** Major functional groups in venlafaxine HCL.

| Sr. No | Functional group | Reported value | Venlafaxine HCl |
|---|---|---|---|
| 1 | OH | 3300-3400 | 3481.51 |
| 2 | C6H5 | 1500-1600 | 1562.87 |
| 3 | Aliphatic CH | 2800-3000 | 2852.72 |
| 4 | C-O-C | 1000-1200 | 1135.46 |

### 5.2 Differential scanning calorimetry

The endothermic peak obtained in thermogram of venlafaxine at 217°C can be attributed to melting of venlafaxine HCl, same was reproduced in thermogram of pellets while the additional endotherm at 246°C represents peak of MCC. Thus, the thermogram showed that the venlafaxine HCl, Eudragit and PVP K-30 are compatible with each other since there is no significant difference in endothermic peak of pure drug (fig 2) and coated pellets.

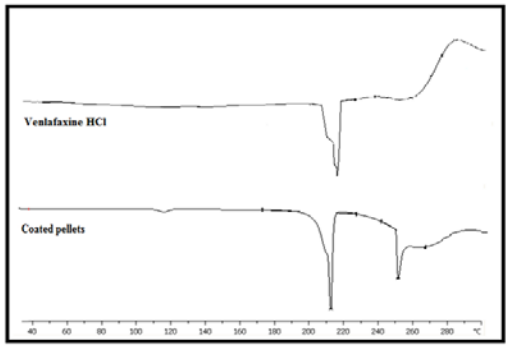


**Fig 2:** DSC thermogram of venlafaxine hydrochloride and coated pellets

### 5.3 % Coating efficiency

The % coating efficiency for all batches were calculated and shown in Table 7. For the film coating, limit for % coating efficiency is 90-95%. Among all the formulations f5, f6, f8 and f9 were in the limit. Formulation f9 has achieved highest coating efficiency.

**Table 7:** % coating efficiency of formulations (f1-f9)

| Batch no | % coating efficiency |
|---|---|
| F1 | 83.87±0.19 |
| F2 | 82.62±0.36 |
| F3 | 79.16±0.32 |
| F4 | 86.95±0.31 |
| F5 | 91.82±0.51 |
| F6 | 93.61±0.24 |
| F7 | 87.43±0.29 |
| F8 | 90.02±0.33 |
| F9 | 94.62±0.41 |

### 5.4 Optimization

**Statistical analysis**

The equations obtained for the $3^2$ factorial design for % drug content and %drug release at 12th hour were as follows:

**1) For %Drug content**

$33.70+5.28*A+2.03*B-0.82*AB+0.45*A^2-0.80B^2$

**2) For % drug release at 12th hour**

$65.21+5.53*A+17.11*B+2.00*AB-2.95*A^2+5.25B^2$

**Table 8:** Adequate precision

| Responses | f-value | p-value | Adequate precision | Predicted value | Experimental value | % Error |
|---|---|---|---|---|---|---|
| % Drug content | 37.06 | 0.0067 | 17.39 | 39.84 | 40.2 | -0.38 |
| % Drug release at 12th hour | 22.94 | 0.0135 | 13.18 | 94.14 | 92.8 | 1.34 |

For % drug content and % drug release at 12th hour, the model F-value was found to be 37.06and 22.94 respectively which implies the model is significant. P-value which is less than 0.05 indicates model terms are significant. Adequate precision shows signal to noise ratio shown in table 12. The $R^2$ value for %drug content and % drug release at 12th hour was found to be0.984 and 0.974 respectively.

### Response surface analysis

By using $3^2$ factorial design, nine batches of venlafaxine hydrochloride drug layered pellets were prepared by solution layering technology varying two independent variables, polymer (Eudragit RLPO) and binder (PVP K-30). The %drug release at 12th hour and % drug content were taken as the dependent variables were determined. A substantial high drug release and high drug content was achieved in f9 formulation which is similar to that of marketed product (Venlor- XR)

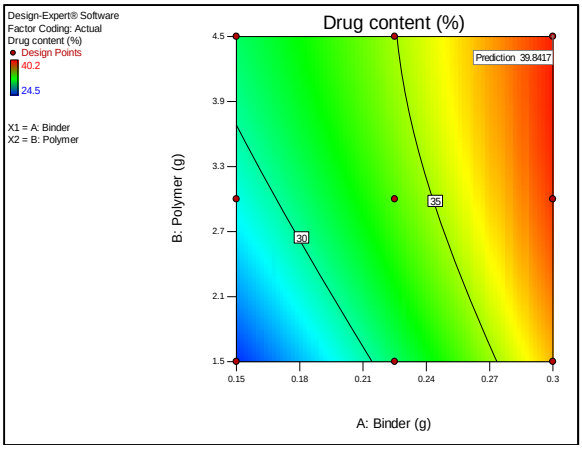


**Fig 3:** Counter plot showing the influence of amount of polymer and amount of binder on the % drug content

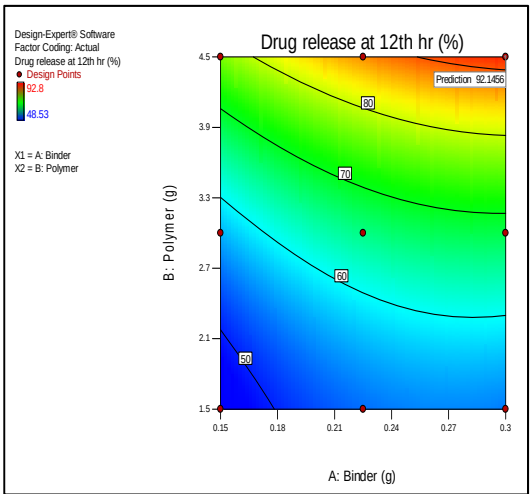


**Fig 4:** Counter plot showing the influence of amount of polymer and amount of binder on the % drug release of venlafaxine hydrochloride at 12th hour.

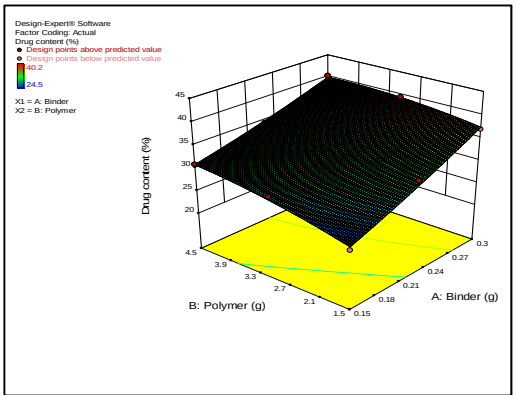


**Fig 5:** Response surface plot showing the influence of amount of polymer and amount of binder on the % drug release at 12th hour of venlafaxine HCl

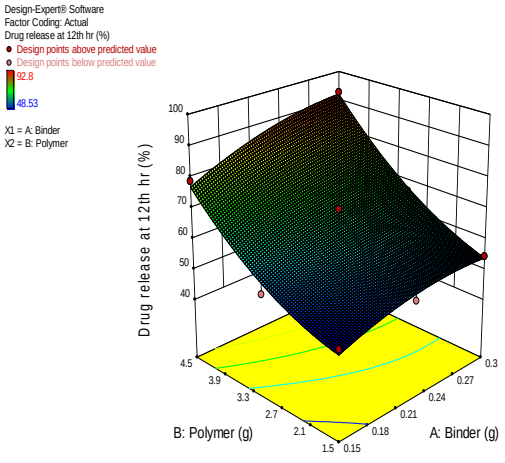


**Fig 6:** Response surface plot showing the influence of amount of polymer and amount of binder on the % drug content of venlafaxine HCl

## 5.6 Flow properties

All the formulated batches were found to be within the I.P limit and hence they show excellent flow properties**.** Flow properties for all the formulations were found to be as follows:

**Table 9:** Flow properties for the coated venlafaxine HCl pellets

| Batch No | Angle of repose | Bulk density | Tapped density | Carr's index | Housner's index |
|---|---|---|---|---|---|
| f1 | 23.26 | 0.60 | 0.65 | 7.69 | 1.08 |
| f2 | 25.64 | 0.66 | 0.72 | 8.33 | 1.09 |
| f3 | 23.74 | 0.68 | 0.73 | 6.84 | 1.07 |
| f4 | 21.80 | 0.72 | 0.76 | 5.26 | 1.05 |
| f5 | 25.64 | 0.73 | 0.77 | 6.49 | 1.05 |
| f6 | 23.74 | 0.70 | 0.73 | 4.10 | 1.04 |
| f7 | 21.74 | 0.72 | 0.77 | 6.49 | 1.06 |
| f8 | 25.37 | 0.66 | 0.71 | 7.04 | 1.07 |
| f9 | 22.21 | 0.64 | 0.71 | 9.85 | 1.10 |

## 5.7. % Drug content

Drug content of all the formulations was found to be between 24.55 to 40.23% Table 10. Maximum drug content was found in batch no 9.

**Table 10:** % drug content of formulations (f1-f9)

| Batch no | Theoretical drug content (%) | Actual drug content (%) |
|---|---|---|
| F1 | 42 | 24.55±0.12 |
| F2 | | 32.00±0.23 |
| F3 | | 37.00±0.31 |
| F4 | | 29.51±0.18 |
| F5 | | 33.00±0.17 |
| F6 | | 39.57±0.15 |
| F7 | | 31.00±0.21 |
| F8 | | 34.6.±0.32 |
| F9 | | 40.23±0.34 |

## 5.8 *In-vitro* drug release

The release of drug from the developed formulations (f1-f9) and marketed formulation (VENLOR XR) was determined and shown fig 7. *In-vitro* percentage drug release from the pellets formulations f1-f9 using different concentrations of Eudragit RLPO and PVP K-30 showed 48.53%, 51.1%, 54.4%, 63.2%, 69.86%, 66.66%, 78.93%, 85.06%, 92.8% and 91.2 respectively. Among all f9 was found to be best formulation which sustains the drug release rate of venlafaxine hydrochloride from formulation f9 and marketed formulation was compared and the results were reported graphically.

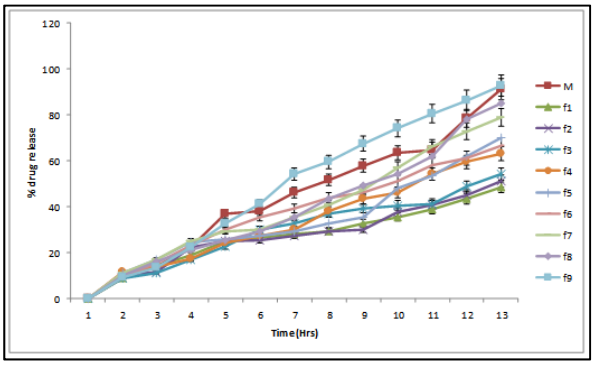


**Fig 7:** *In-vitro* drug release of formulations (f1-f9)

## 5.9 Comparative dissolution profile of optimized formulation and marketed formulation:

From the *in-vitro* release data obtained by dissolution studies. Formulation f9 was selected as optimized formulation. The dissolution profile of the optimized

formulation of sustained release pellets was compared with marketed formulation shown in fig 8.

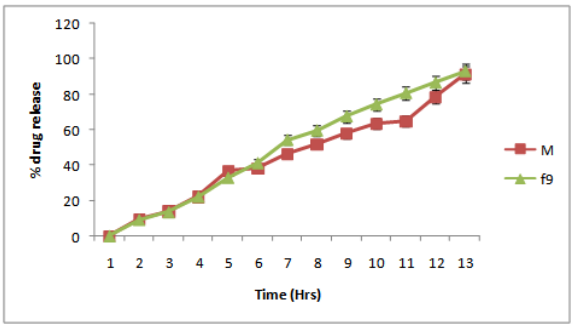


**Fig 8:** Comparative dissolution profile of optimized and marketed formulation

The similarity factor (f2) which was calculated between the marketed and formulation f9 was found to be 81.2. Therefore optimized batch and marketed formulation showed similar release profile.

Table 11: Similarity factor for optimized and marketed formulation

| Optimized formulations | $f_2$ value | Consideration |
|---|---|---|
| Optimized batch | 81.2 | Similar |

### 6.0 Drug release mechanism

Regression analysis was performed and best fits were calculated on the basis of correlation factors as $R^2$shown in Table 12. The best fit model for optimized batch f9 was found to be zero order release model.

**Table 12:** $R^2$ value for release kinetics model

| Model name | $R^2$ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Zero order model | 0.960 | 0.995 | 0.969 | 0.991 | 0.950 | 0.984 | 0.982 | 0.978 | 0.992 |
| First order model | 0.627 | 0.634 | 0.682 | 0.700 | 0.664 | 0.665 | 0.692 | 0.732 | 0.737 |
| Higuchi-diffusion model | 0.970 | 0.933 | 0.957 | 0.925 | 0.876 | 0.966 | 0.903 | 0.876 | 0.929 |
| Kosmeyer-peppas model | 0.742 | 0.732 | 0.795 | 0.772 | 0.739 | 0.789 | 0.773 | 0.807 | 0.850 |

### 6.1 Scanning electron microscopy

The surface morphology of venlafaxine HCl pellets and blank pellets were studied by SEM. The morphology of pellets was observed to be smooth and spherical. The coating of coated pellets was observed uniform shown in fig 9 and 10.

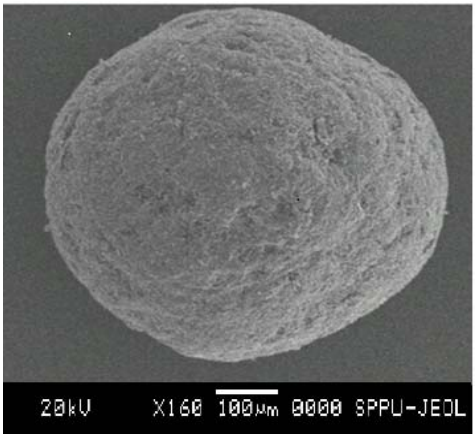


**Fig 9:** Surface morphology of uncoated pellets.

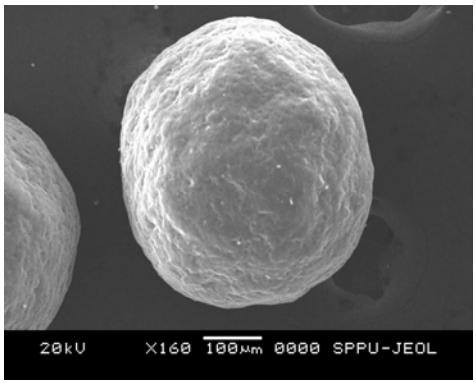


**Fig 10:** Surface morphology of venlafaxine HCl coated pellets.

### 6. Conclusion

In the present research work, systematic efforts were made to prepare coated venlafaxine HCl pellets by solution layering technique. The coated pellets were evaluated for flow properties, %drug content, % drug release at 12$^{th}$ hour and found to be within the Indian Pharmacopial limits. This work was demonstrated for $3^2$ factorial design, contour plots and 3D surface plots of optimized batch were derived. Based on the evaluation parameters and dissolution studies, it was concluded that f9 batch was finalized as optimized formulation. The optimized formulation (f9) shows highest % drug release and % drug content. The optimized formulation of venlafaxine HCl was characterized by SEM analysis to understand surface morphology, indicating the uniform coating of the pellets. DSC and FTIR data showed that no interaction takes place between venlafaxine HCl, Eudragit RLPO and PVP K-30.Therefore; the present Venlafaxine HCl pellets are similar to marketed product.

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