

Comparative Evaluation of Matrix-Polymer Type and Concentration on the In Vitro Release of Venlafaxine Hydrochloride Extended-Release Matrix Tablets

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Abstract: Venlafaxine hydrochloride is a highly water-soluble antidepressant that has historically been administered in multiple daily doses in its immediate-release form. Extended-release matrix systems can reduce dosing frequency by controlling drug release over an extended period. The objective of the study was to formulate and evaluate venlafaxine hydrochloride extended-release matrix tablets using hydrophilic and hydrophobic release-retarding polymers and to investigate the influence of polymer type and concentration on in vitro drug-release behavior.

1. INTRODUCTION

Venlafaxine hydrochloride is a serotonin–norepinephrine reuptake inhibitor used in the management of depressive and anxiety-related disorders. Because the immediate-release drug has a relatively short elimination half-life, multiple daily administration may be required to maintain therapeutic exposure. Extended-release dosage forms are designed to provide prolonged drug release and reduce the frequency of administration.

Matrix tablets are among the commonly investigated oral modified-release systems. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) hydrate on contact with aqueous media and form a viscous gel layer through which drug diffusion and polymer erosion can occur. Hydrophobic polymers can reduce water penetration and thereby further retard drug release.

Venlafaxine hydrochloride is highly water soluble, which makes achieving prolonged release from a conventional hydrophilic matrix technically challenging. Previous studies have investigated HPMC, ethyl cellulose, Eudragit polymers, waxes, ion-exchange resins, coated systems, and combinations of hydrophilic and hydrophobic materials for controlling venlafaxine release. Therefore, the formulation behavior of venlafaxine matrix systems depends strongly on polymer type, polymer concentration, drug loading, and matrix structure.

Earlier research had already established sustained-release venlafaxine systems before the present project was conducted. For example, Makhija and Vavia reported once-daily sustained-release venlafaxine tablets using different matrix and polymeric approaches. Subsequent studies investigated combinations of HPMC and hydrophobic polymers and applied factorial/response-surface approaches to optimize sustained release. A later comparative study specifically evaluated hydrophilic, hydrophobic, and waxy matrix formers for venlafaxine hydrochloride.

The purpose of the study was to comparatively evaluate the effect of matrix-polymer type and concentration on venlafaxine hydrochloride release using three polymer systems: Eudragit RL 100, HPMC K4M, and HPMC K15M.

Research Methodology

Venlafaxine hydrochloride matrix tablets containing 225 mg drug per tablet were prepared by wet granulation. Three release-retarding polymers—Eudragit RL 100, HPMC K4M, and HPMC K15M—were investigated at three concentrations (15%, 20%, and 25% w/w), producing nine formulations (F1–F9). The prepared granules were evaluated for flow properties, and the tablets were evaluated for weight variation, thickness, hardness, friability, and drug content. In vitro dissolution testing was performed using USP apparatus II in phosphate buffer pH 6.8 at $37 \pm 0.5^\circ\text{C}$ and 50 rpm for 24 h. The formulation containing 25% Eudragit RL 100 (F7) was further evaluated using zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. Three-month accelerated stability data for F7 were also evaluated.

Results

All nine formulations exhibited acceptable granule-flow properties and tablet characteristics. Drug content ranged from 97.16% to 102.60%. Increasing the concentration of the release-retarding polymer generally reduced the rate of venlafaxine release. Among the evaluated formulations, F7 containing 25% Eudragit RL 100 provided the most prolonged release, reaching 95.41% drug release at 24 h. For F7, the dissolution data showed a strong linear relationship with the zero-order model ($R^2 = 0.9992$), while Higuchi analysis also showed a strong fit ($R^2 = 0.9746$). When the Korsmeyer–Peppas model was applied to the initial portion of the release profile through approximately 60% drug release, the release exponent was approximately 0.780 ($R^2 = 0.9986$), consistent with

anomalous/non-Fickian transport for a cylindrical matrix under the applicable model assumptions. After three months at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$, the reported drug release and assay values of F7 remained within the study specifications.

Conclusion

The study demonstrates that matrix-polymer type and polymer concentration influence the release of venlafaxine hydrochloride from matrix tablets. Among the evaluated formulations, F7 containing 25% Eudragit RL 100 produced the most prolonged in vitro release profile. The work is best interpreted as a comparative formulation and release-behavior study rather than as a claim of novel venlafaxine extended-release technology.

Keywords: Venlafaxine hydrochloride; extended-release tablets; matrix tablets; Eudragit RL 100; HPMC K4M; HPMC K15M; dissolution; drug-release kinetics.

2. Materials and Methods

2.1 Materials

Venlafaxine hydrochloride was obtained from Dr. Reddy's Laboratories, Hyderabad, India. HPMC K4M and HPMC K15M were obtained from Cadila Pharmaceuticals, Ahmedabad, India. Eudragit RL 100 was obtained from S.D. Fine-Chem Ltd., Mumbai, India. Mannitol, microcrystalline cellulose, polyvinylpyrrolidone K30, and colloidal silicon dioxide were used as pharmaceutical excipients.

2.2 Formulation design

Nine formulations were prepared using three matrix-forming polymers at three concentrations.

Formulation	Polymer	Polymer concentration
F1	Eudragit RL 100	15%
F2	HPMC K4M	15%
F3	HPMC K15M	15%
F4	Eudragit RL 100	20%
F5	HPMC K4M	20%
F6	HPMC K15M	20%
F7	Eudragit RL 100	25%
F8	HPMC K4M	25%
F9	HPMC K15M	25%

Each tablet contained 225 mg of venlafaxine hydrochloride and had a target weight of 600 mg.

2.3 Composition

Ingredient (mg/tablet)	F1/F4/F7	F2/F5/F8	F3/F6/F9
Venlafaxine HCl	225	225	225
MCC	72	72	72
Mannitol	177/147/87*	177/147/87*	177/147/87*
Eudragit RL 100	90/120/180*	—	—
HPMC K4M	—	90/120/180*	—
HPMC K15M	—	—	90/120/180*
PVP K30	24	24	24
Colloidal silicon dioxide	12	12	12
Total	600	600	600

*The three quantities correspond to the 15%, 20%, and 25% polymer levels, respectively.

2.4 Preparation of matrix tablets

The drug, polymer, microcrystalline cellulose, and mannitol were passed through a suitable sieve and mixed uniformly. PVP K30 was used as binder. The blend was wet granulated, and the wet mass was passed through a suitable sieve and dried. The dried granules were resized and lubricated before compression. Tablets were compressed using a rotary tablet compression machine.

2.5 Pre formulation studies

The drug substance was evaluated for appearance, melting point, solubility, UV absorption characteristics, and drug–excipient compatibility.

The observed melting point was 215–217°C compared with the reported value of approximately 216°C.

Venlafaxine hydrochloride was reported to be soluble in water, freely soluble in methanol, soluble in dimethylformamide, and sparingly soluble in methylene chloride.

2.6 UV spectrophotometric analysis

Venlafaxine hydrochloride showed a maximum absorbance at 226 nm in the analytical conditions reported in the original study.

The calibration data were:

Concentration (µg/mL)	Absorbance
0	0.000
2	0.097
4	0.194
6	0.289
8	0.384
10	0.480
12	0.586

Regression of the archived calibration data gave:

$$A = 0.04846C - 0.00079 \text{ with: } R^2 = 0.99980$$

where A is absorbance and C is concentration in µg/mL.

2.7 Evaluation of granules

Bulk density, tapped density, Carr's compressibility index, Hausner ratio, and angle of repose were determined. The archived values were:

Formulation	Bulk density (g/mL)	Tapped density (g/mL)	Carr index (%)	Hausner ratio	Angle of repose (°)
F1	0.510	0.598	15.81	1.17	26.28
F2	0.512	0.597	15.38	1.18	26.85
F3	0.512	0.600	14.87	1.17	27.14
F4	0.505	0.591	14.64	1.17	27.75
F5	0.507	0.595	14.72	1.17	28.07
F6	0.508	0.597	14.97	1.18	28.07
F7	0.512	0.595	13.85	1.16	29.39
F8	0.515	0.598	13.91	1.16	29.74
F9	0.515	0.602	14.43	1.17	29.02

Overall, the granules exhibited acceptable flow characteristics according to the classification used in the original study.

2.8 Evaluation of tablets

The prepared tablets were evaluated for average weight, thickness, hardness, friability, and drug content.

Formulation	Average weight (mg)	Diameter (mm)	Hardness (kg/cm ²)	Friability (%)	Thickness (mm)
F1	597	12.5	7.1	0.11	6.1
F2	598	12.5	7.3	0.06	6.5
F3	596	12.5	7.6	0.14	5.8
F4	601	12.5	7.5	0.04	6.9
F5	601	12.5	7.1	0.14	6.8
F6	598	12.5	7.2	0.06	6.7
F7	599	12.5	6.9	0.16	6.8
F8	605	12.5	6.8	0.41	6.8
F9	602	12.5	7.2	0.02	6.9

The archived drug-content results ranged from 97.16% to 102.60%.

2.9 In vitro dissolution study

Dissolution testing was conducted using USP apparatus II (paddle) with 900 mL phosphate buffer pH 6.8 at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. Samples were withdrawn at predetermined intervals and replaced with fresh dissolution medium. Samples were filtered and analyzed spectrophotometrically at 226 nm.

3.0 Results and Discussion

3.1 Effect of polymer type and concentration

The dissolution data demonstrated that polymer type and polymer concentration affected the release of venlafaxine hydrochloride.

At 15% polymer concentration, F1, F2, and F3 released approximately 95%, 92%, and 94% of drug by 12 h, respectively.

Increasing the polymer concentration to 20% prolonged release. F4 reached 96.66% release at 18 h, whereas F5 and F6 reached approximately 97% by 16 and 14 h, respectively.

At 25% polymer concentration, F7 showed the most prolonged release, reaching 95.41% at 24 h. F8 and F9 showed faster release than F7, with approximately 96.46% and 97.49% release by 20 h, respectively.

These findings demonstrate that increasing the concentration of the release-retarding polymer generally increased the resistance to drug release. The effect was particularly pronounced for the Eudragit RL 100 formulations.

The behavior is consistent with the general principle that increasing the concentration of a matrix-forming polymer can increase the diffusional path length and/or reduce the effective penetration of dissolution medium into the matrix. However, the exact release mechanism depends on polymer hydration, permeability, swelling, erosion, tablet structure, and drug solubility.

3.2 F7 dissolution profile

F7, containing 25% Eudragit RL 100, produced the most prolonged release profile among the evaluated formulations:

Time (h)	Cumulative drug release (%)
2	12.70
4	20.62
6	29.37
8	35.83
10	43.54
12	50.41
14	57.50
16	64.58
18	73.12
20	82.08
24	95.41

The absence of an abrupt initial release in this profile indicates that the matrix provided substantial resistance to immediate drug dissolution under the experimental conditions.

4.0 Drug-release kinetic analysis of F7

The F7 dissolution profile was fitted to several mathematical models.

Zero-order model

Regression of cumulative percentage drug release against time gave:

$$Q = 3.747t + 5.731$$

with: $R^2 = 0.9992$

This was the strongest fit among the evaluated full-profile models and indicates an approximately linear cumulative release profile over the studied period.

First-order model

Regression of log percentage drug remaining against time gave:

$$R^2 = 0.8387$$

indicating a substantially poorer fit than the zero-order model.

Higuchi model

Regression of cumulative percentage drug release against the square root of time gave:

$$R^2 = 0.9746$$

indicating a good relationship between release and square root of time.

Hixson–Crowell model

The archived data gave:

$$R^2 \approx 0.9323$$

which was lower than the zero-order and Higuchi fits.

Korsmeyer–Peppas model

The Korsmeyer–Peppas model was applied only to the initial release region up to approximately 60% drug release, as appropriate for the model.

The calculated release exponent was approximately:

$$n = 0.780$$

with: $R^2 = 0.9986$

For a cylindrical matrix, this value is consistent with anomalous/non-Fickian transport under the assumptions of the model, indicating that drug diffusion and polymer relaxation/erosion may both contribute to release.

5.0 Drug–excipient compatibility

FTIR studies were performed on venlafaxine hydrochloride and selected drug–excipient physical mixtures. The original thesis reported retention of the characteristic drug spectral features in the physical mixtures and interpreted this as an absence of significant interaction.

6.0 Stability study

The selected formulation F7 was subjected to accelerated stability evaluation at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$ for three months.

Parameter	Initial	1 month	2 months	3 months	Study specification
Drug release (%)	95.41	95.32	95.10	94.89	$\geq 85\%$
Assay (%)	95.31	95.18	94.82	94.56	90–110%

The changes in drug release and assay over three months were relatively small and remained within the specifications stated in the original study.

7.0 Limitations

Several limitations should be acknowledged.

First, the formulation experiments were originally performed in 2012–2013; therefore, the work should be presented as a study based on the original experimental dataset rather than as a newly performed 2026 formulation study.

Second, the available dissolution dataset contains mean values but does not currently provide the underlying replicate-level dissolution observations. Consequently, formal statistical comparison among formulations cannot be reconstructed reliably from the summary values alone.

Third, the original analytical method was UV spectrophotometry. Before publication, the analytical method should be reverified for specificity in the presence of dissolution medium and excipients, and preferably confirmed using a validated chromatographic method if available.

Fourth, the study did not use a formal quality-by-design optimization strategy.

Finally, previous publications and patents have already described multiple venlafaxine extended-release technologies, including hydrophilic/hydrophobic matrix systems and coated systems. Therefore, the present work should not claim novelty solely from the use of HPMC or Eudragit polymers.

8. Conclusion

Venlafaxine hydrochloride extended-release matrix tablets were prepared using Eudragit RL 100, HPMC K4M, and HPMC K15M at concentrations of 15%, 20%, and 25%. The type and concentration of matrix polymer influenced the rate and duration of drug release.

Among the archived formulations, F7 containing 25% Eudragit RL 100 provided the most prolonged in vitro release profile, with 95.41% drug release after 24 h under the experimental dissolution conditions. The F7 profile showed a strong fit to the zero-order model and a good fit to the Higuchi model. Application of the Korsmeyer–Peppas model to the initial release region yielded an exponent of approximately 0.780, suggesting anomalous/non-Fickian release behavior.

The stability results showed that F7 maintained assay and dissolution performance within the study specifications during three months of accelerated storage.

Because comparable venlafaxine extended-release matrix technologies have previously been reported, the principal contribution of the present work is the comparative evaluation of polymer type and concentration and their relationship with the in vitro release behavior of venlafaxine hydrochloride. Confirmatory experimentation using the optimized formulation and a validated analytical method would strengthen the scientific basis of the manuscript.

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