Formulation Development and In-vitro Characterization of Extended Release Venlafaxine HCl Pellets

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Abstract-This study aimed to develop and characterize extended-release (ER) pellets of Venlafaxine Hydrochloride (HCl), an antidepressant, to achieve prolonged therapeutic action compared to immediate-release formulations, with pharmaceutical equivalence to the innovator product, Effexor XR®. The formulation process utilized the Wurster fluid bed coating technique, incorporating ethyl cellulose and medium-chain triglycerides as key excipients to control drug release. Preformulation studies confirmed the compatibility of Venlafaxine HCl with excipients through physical and analytical assessments. Seven trial formulations were prepared, with formulations T6 and T7 optimized based on evaluation parameters, including percentage yield, bulk density, loss on drying, water content, and drug content. In vitro dissolution studies demonstrated that T6 and T7 achieved 88–92% drug release over 20 hours, following first-order kinetics and the Higuchi matrix model, indicative of a super case II transport mechanism. The similarity factor (f2) ranged from 69 to 77, confirming equivalence to Effexor XR®. Stability studies, conducted per ICH guidelines under accelerated (40±2°C/75±5% RH) and long-term (25±2°C/60±5% RH) conditions for 30 and 90 days, respectively, revealed no significant changes in physicochemical properties. The optimized formulations (T6 and T7) effectively minimized dose dumping and provided a release profile suitable for once-daily administration, offering a viable generic alternative to Effexor XR®.

Keywords-Venlafaxine Hydrochloride, extended-release pellets, fluid bed coating, ethyl cellulose, medium-chain triglycerides, dissolution, release kinetics, stability, pharmaceutical equivalence, Effexor XR®

INTRODUCTION

Venlafaxine Hydrochloride (HCl), a widely used antidepressant, is typically administered as an immediate-release dosage form, which often requires multiple daily doses due to its short half-life and results in fluctuating plasma concentrations. These fluctuations can lead to suboptimal therapeutic outcomes and potential side effects, including dose dumping, where an exaggerated drug release occurs prematurely, causing adverse effects. To address these challenges, extended-release (ER) formulations have emerged as a promising strategy to provide sustained drug release, improve patient compliance, and enhance therapeutic efficacy by maintaining consistent plasma levels over an extended period. This study focuses on the development of ER pellets of Venlafaxine HCl, designed to be pharmaceutically equivalent to the innovator product, Effexor XR®, using the Wurster fluid bed coating technique. By incorporating polymers such as ethyl cellulose and medium-chain triglycerides, the formulation aims to control drug release, minimize dose dumping, and achieve a release profile suitable for once-daily administration. The research encompasses preformulation studies, formulation optimization, in vitro characterization, release kinetics evaluation, and stability testing per ICH guidelines to ensure the development of a robust and effective generic product.

LITERATURE REVIEW

The development of extended-release (ER) formulations for Venlafaxine Hydrochloride (HCl), a serotonin-norepinephrine reuptake inhibitor (SNRI) used in the treatment of depression, has been extensively explored to overcome the limitations of immediate-release dosage forms, such as frequent dosing and risk of dose dumping. This review summarizes key studies and advancements in the formulation, characterization, and evaluation of Venlafaxine HCl ER pellets, focusing on pelletization techniques, polymer coatings, and in vitro performance.

Ajay et al. (2018) formulated Venlafaxine HCl ER pellets using commercially available sugar spheres coated with ethyl cellulose N-50 to achieve a 20-hour

drug release profile. The study optimized formulations by increasing ethyl cellulose and plasticizer concentrations, demonstrating controlled initial drug release and equivalence to the innovator product, Effexor XR®. The use of ethyl cellulose provided superior dissolution profiles compared to polymers like Eudragit NE 30 D, highlighting the critical role of polymer type and concentration in modulating drug release.

Bhalekar and Madgulka (2017) developed Venlafaxine HCl ER pellets via solution layering, evaluating flow properties, drug content, and 12-hour drug release, all of which met Indian Pharmacopoeial standards. Scanning Electron Microscopy (SEM) confirmed uniform coating, while Differential Scanning Calorimetry (DSC) and Fourier-Transform Infrared Spectroscopy (FTIR) analyses indicated no interactions between Venlafaxine HCl, Eudragit RLPO, and PVP K-30, suggesting compatibility with the selected excipients and similarity to marketed products.

Redasani et al. (2017) validated a sensitive and precise analytical method for estimating Venlafaxine HCl in bulk and capsule forms, adhering to ICH guidelines. The method's reproducibility and lack of excipient interference underscored its applicability for quality control in ER pellet formulations.

Brahmareddy et al. (2015) standardized the manufacturing process for Venlafaxine HCl 150 mg ER pellets, achieving stability under accelerated conditions for one month. The optimized formulations exhibited in vitro release profiles comparable to the U.S. marketed product, emphasizing the reproducibility of the pelletization process.

Arora et al. (2014) explored ER pellets using ethyl cellulose and Acryl-EZE, noting poor spheroid yield due to fines generation. Substituting Hypromellose with Povidone K30 as a binder improved yield and achieved a release profile similar to the reference listed drug (RLD). Increasing ethyl cellulose coating from 7.5% to 8.5% w/w controlled initial drug release without significantly affecting the 12-hour release profile, indicating that coating thickness is a critical parameter.

Yuan et al. (2014) highlighted the advantages of multiparticulate systems, such as coated pellets, in reducing dose dumping and improving absorption predictability. Their work on liquid oral sustained-release suspensions emphasized the role of pellet-based systems in minimizing local irritation and enhancing bioavailability.

Abbaspour et al. (2014) investigated self-nanoemulsifying drug delivery systems (SNEDDS) for loratadine using extrusion-spheronization, demonstrating higher in vitro release compared to liquid SNEDDS and powder tablets. This approach validated the scalability of pelletization for improving dissolution and solubility, applicable to Venlafaxine HCl formulations.

Katakam et al. (2014) formulated Venlafaxine HCl sustained-release tablets using hydrophilic and hydrophobic polymer combinations (e.g., Carbopol 71G, HPMC K15M, Eudragit RS100). The formulation with Carbopol 71G, xanthan gum, and microcrystalline cellulose extended drug release and remained stable under accelerated conditions, suggesting the potential of polymer blends for ER pellets.

Kamari et al. (2013) emphasized the growing importance of pellet-based formulations for pediatric and geriatric populations due to their ease of administration and patient compliance. The study highlighted the flexibility of pellets in achieving tailored release profiles, supporting their application in Venlafaxine HCl delivery.

Patil et al. (2013) developed sustained-release matrix tablets of Venlafaxine HCl using Carbopol 971P and ethyl cellulose, achieving 95.47% drug release with a diffusion-controlled mechanism (Korsmeyer-Peppas model). This study underscored the efficacy of matrix systems, which can be adapted to pellet formulations for controlled release.

MSrujan et al. (2012) noted that ER pellets offer advantages such as high surface area, rapid systemic absorption, and no drug accumulation, making them superior to tablets in terms of release consistency and bioavailability.

Battula et al. (2012) developed a rapid, sensitive HPLC method for Venlafaxine HCl quantification, with a linear range of 2–50 µg/mL, supporting accurate analysis in ER pellet development.

Lavanya et al. (2011) reviewed pelletization as a promising drug delivery system, citing its portability, compliance, and flexibility in formulation as tablets or capsules. The technology's applicability to both oral and buccal routes further enhances its relevance for Venlafaxine HCl.

Muschert et al. (2009) investigated drug release mechanisms in ethyl cellulose-coated pellets, confirming that diffusion through intact polymeric membranes controls release, independent of drug solubility or core type. This finding supports the use of ethyl cellulose in Venlafaxine HCl ER pellets for consistent release profiles.

Overall, the literature underscores the efficacy of pelletization techniques, particularly fluid bed coating with ethyl cellulose, in developing Venlafaxine HCl ER formulations. These studies highlight the importance of polymer selection, coating optimization, and rigorous evaluation to achieve controlled release, stability, and equivalence to innovator products, guiding the current research in formulating a generic Venlafaxine HCl ER pellet product.

DRUG AND EXCIPIENT PROFILE

Drug Profile: Venlafaxine Hydrochloride (HCl)

Venlafaxine Hydrochloride (HCl) is a serotonin-norepinephrine reuptake inhibitor (SNRI) widely used as an antidepressant for the treatment of major depressive disorder, generalized anxiety disorder, and other mood-related conditions. Its chemical structure and physicochemical properties are critical for designing effective extended-release (ER) formulations.

Chemical Structure

Venlafaxine HCl is chemically described as (±)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol hydrochloride. Its molecular formula is $C_{17}H_{27}NO_2 \cdot HCl$, with a molecular weight of 313.86 g/mol.

Physicochemical Properties

- Appearance: White to off-white crystalline powder.
- Melting Point: 215–217°C, determined by capillary tube method.
- Solubility: Freely soluble in water and methanol, soluble in ethanol, slightly soluble in acetone, and practically insoluble in neutral solvents. Solubility was assessed using the saturation shake flask method, followed by HPLC analysis.
- pKa: Approximately 9.4, indicating weak basicity.
- Log P: 3.28, suggesting moderate lipophilicity, which supports its suitability for ER formulations.
- BCS Classification: Class I (high solubility, high permeability), though bioavailability is limited to 42±5% due to first-pass metabolism.
- Stability: Stable under standard storage conditions but susceptible to degradation under extreme pH or high humidity, necessitating protective coatings in ER formulations.

Pharmacological Properties

- Mechanism of Action: Inhibits reuptake of serotonin and norepinephrine, with weak dopamine reuptake inhibition.
- Half-Life: Approximately 5 hours for venlafaxine and 11 hours for its active metabolite, O-desmethylvenlafaxine, justifying the need for ER formulations to reduce dosing frequency.
- Therapeutic Use: Effective for depression, anxiety, and panic disorders, with ER formulations improving patient compliance through once-daily dosing.

Excipient Profile

The following excipients were used in the formulation of Venlafaxine HCl ER pellets, selected for their compatibility and role in achieving controlled release and pellet stability.

1. Sugar Spheres (#20–#25)

- Description: Inert spherical pellets composed of sucrose and starch, used as starter cores for drug layering.
- Physicochemical Properties:
  - Particle Size: 710–850 µm (ASTM #20–#25).
  - Appearance: White to off-white, free-flowing spherical beads.
  - Solubility: Soluble in water, providing a stable, inert substrate for coating.
  - Bulk Density: Approximately 0.8–0.9 g/cm³, ensuring good flow properties.
  - Moisture Content: Low (<2%), minimizing degradation risks during coating.
- Function: Serve as a core for drug layering, providing a uniform surface for coating and ensuring consistent pellet size and shape.
- Compatibility: No chemical interactions with Venlafaxine HCl, confirmed through physical appearance studies under accelerated conditions.

2. Ethyl Cellulose (10 cps and 20 cps)

- Description: A water-insoluble, non-ionic cellulose ether used as a rate-controlling polymer for ER coatings.
- Physicochemical Properties:
  - Appearance: White to off-white powder.
  - Viscosity: 10 cps and 20 cps grades, determining coating thickness and release rate.
  - Solubility: Insoluble in water, soluble in organic solvents like isopropyl alcohol.
  - Molecular Weight: Varies with viscosity grade, typically 50,000–200,000 g/mol.
  - Glass Transition Temperature: ~130°C, ensuring film integrity during processing.
- Function: Forms a diffusion-controlled barrier for sustained drug release, reducing dose dumping. Higher viscosity (20 cps) provides thicker coatings for extended release.
- Compatibility: Stable with Venlafaxine HCl, as confirmed by DSC and FTIR studies showing no interactions.

3. Talc
- Description: A hydrated magnesium silicate used as an anti-tacking agent and lubricant.
- Physicochemical Properties:
  - Appearance: Fine, white to off-white powder.
  - Particle Size: Typically <45 µm, ensuring uniform dispersion in coating solutions.
  - Solubility: Insoluble in water and organic solvents.
  - Specific Gravity: 2.7–2.8 g/cm³.
  - Moisture Content: Low (<0.5%), suitable for moisture-sensitive formulations.
- Function: Prevents pellet agglomeration during coating and aids lubrication during capsule filling or tableting.
- Compatibility: No interactions with Venlafaxine HCl, as evidenced by physical stability studies.

4. Medium-Chain Triglycerides (MCT)
- Description: A mixture of triglycerides with fatty acid chains of 6–12 carbons, used as a plasticizer.
- Physicochemical Properties:
  - Appearance: Clear, colorless to pale yellow liquid.
  - Solubility: Insoluble in water, soluble in organic solvents like isopropyl alcohol.
  - Viscosity: Low (~25–33 mPa·s at 20°C), facilitating uniform coating application.
  - Density: 0.93–0.96 g/cm³.
  - Boiling Point: >200°C, stable under coating conditions.
- Function: Enhances flexibility of ethyl cellulose coatings, improves intestinal absorption, and aids in achieving uniform film formation.
- Compatibility: Compatible with Venlafaxine HCl, with no observed chemical interactions in stability studies.

5. Water
- Description: Purified water used as a solvent in drug layering and coating solutions.
- Physicochemical Properties:
  - Appearance: Clear, colorless liquid.
  - Purity: Meets USP standards for purified water, free of impurities.
  - pH: Neutral (~7.0).
  - Boiling Point: 100°C, suitable for fluid bed drying processes.
- Function: Acts as a co-solvent with isopropyl alcohol to dissolve or suspend formulation components during pellet coating.
- Compatibility: No adverse interactions with Venlafaxine HCl or other excipients, ensuring formulation stability.

6. Isopropyl Alcohol
- Description: A volatile organic solvent used in coating solution preparation.
- Physicochemical Properties:
  - Appearance: Clear, colorless liquid with a characteristic odor.
  - Solubility: Miscible with water, ethanol, and other organic solvents.
  - Boiling Point: 82.5°C, allowing easy evaporation during drying.
  - Density: 0.785 g/cm³.
  - Purity: ≥99%, meeting pharmaceutical-grade standards.
- Function: Dissolves ethyl cellulose and facilitates uniform dispersion of coating materials in the Wurster coating process.
- Compatibility: Evaporates during drying, leaving no residual interactions with Venlafaxine HCl or excipients.

Aim

The primary aim of this study is to develop and evaluate a generic extended-release (ER) solid oral dosage form of Venlafaxine Hydrochloride (HCl) that is pharmaceutically equivalent to the innovator product, Effexor XR®. By utilizing the pelletization technique with the Wurster fluid bed coating method, the formulation seeks to achieve prolonged drug release to enhance therapeutic efficacy, improve patient compliance through once-daily dosing, and minimize dose dumping compared to immediate-release formulations.

OBJECTIVES

Major Objective

- To develop a generic extended-release solid oral dosage form of Venlafaxine HCl that matches the release profile and therapeutic performance of the innovator product, Effexor XR®.

Minor Objectives

- To prepare and optimize Venlafaxine HCl extended-release pellets using ethyl cellulose and medium-chain triglycerides to control drug release.
- To characterize the physicochemical properties of Venlafaxine HCl ER pellets, including percentage yield, bulk density, loss on drying, water content, and drug content.
- To conduct a comparative in vitro release study of Venlafaxine HCl ER pellets against the innovator product to assess pharmaceutical equivalence.
- To evaluate the stability of the optimized formulations under accelerated and long-term conditions as per ICH guidelines.
- To analyze the release kinetics of the optimized formulations to understand the drug release mechanism and ensure consistency with the innovator product.

MATERIALS AND METHODS

Materials

The materials used for the formulation and evaluation of Venlafaxine Hydrochloride (HCl) extended-release (ER) pellets are listed in Table 1.

Table 1: List of Materials Required

Material	Description	Supplier
Venlafaxine HCl	Active Pharmaceutical Ingredient (API), white to off-white powder	Local Supplier
Sugar Spheres (#20–#25)	Inert cores, 710–850 µm	Local Supplier
Ethyl Cellulose (10 cps, 20 cps)	Rate-controlling polymer	Local Supplier
Medium-Chain Triglycerides (MCT)	Plasticizer	Local Supplier
Talc	Anti-tacking agent, lubricant	Local Supplier
Isopropyl Alcohol	Solvent	Local Supplier
Purified Water	Co-solvent	Local Supplier

Equipment

The equipment used for the preparation, coating, and evaluation of the pellets is listed in Table 2.

Table 2: List of Equipment Required

Equipment	Purpose
Fluid Bed Coater (FBC)	Drug layering and ER coating
Sieve Shaker (ASTM #16, #20, #25)	Particle size distribution and sifting
Tap Densitometer (USP Type II)	Bulk and tapped density measurement
Melting Point Apparatus	Melting point determination
High-Performance Liquid Chromatography (HPLC)	Assay and dissolution analysis
Karl Fischer Titrator	Water content determination
Loss on Drying (LOD) Apparatus	Moisture content analysis
Cone Blender	Lubrication of pellets
Vortex Mixer	Solubility studies
Centrifuge	Solubility studies
Ultrasonic Bath	Mobile phase degassing
Analytical Balance	Accurate weighing

METHODOLOGY

Preformulation Studies

Physical Appearance

The physical appearance of Venlafaxine HCl API was assessed by visual observation and recorded as a white to off-white crystalline powder.

Melting Point

The melting point of Venlafaxine HCl was determined using the capillary tube method. A small amount of powdered drug was filled into a capillary tube, sealed, and placed in a melting point apparatus. The observed melting point range was compared with the literature value of 215–217°C.

Solubility

Solubility was evaluated using the saturation shake flask method. Excess Venlafaxine HCl was added to 1 mL of solvent (water, methanol, ethanol, or acetone) and stirred for 72 hours. The mixture was vortexed, centrifuged at 6000 rpm to sediment undissolved material, and filtered through a 0.22 µm Millipore filter. The filtrate was analyzed by HPLC to determine the drug concentration.

Bulk Density and Tapped Density

Apparent bulk density (ρb) was measured by pouring a weighed amount of powder blend into a 100 mL graduated cylinder and noting the bulk volume (Vb). The bulk density was calculated as:

$$\rho b = \text{Mass of powder} / \text{Bulk volume}$$

Tapped density (ρt) was determined using a tap densitometer (USP Type II). The cylinder was tapped (500, 750, or 1250 taps) until the volume stabilized (percentage difference <3%). The tapped density was calculated as:

$$\rho t = \text{Mass of powder} / \text{Tapped volume}$$

Angle of Repose

The angle of repose was determined by forming a cone of the powder blend and measuring the height (H) and radius (R) of the cone. The angle (θ) was calculated using:

$$\tan \theta = H / R$$

Compressibility Index (Carr's Index)

Carr's Index was calculated using bulk and tapped density values:

$$\text{Carr's Index} = [(\text{Tapped Density} - \text{Bulk Density}) / \text{Tapped Density}] \times 100$$

Hausner's Ratio

Hausner's Ratio was calculated to assess flowability:

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

Compatibility Study

Venlafaxine HCl was blended with excipients (sugar spheres, ethyl cellulose, talc, medium-chain triglycerides) in equal ratios and stored under long-term (25±2°C/60±5% RH), intermediate (30±2°C/65±5% RH), and accelerated (40±2°C/75±5% RH) conditions. Physical appearance was evaluated to confirm compatibility, as shown in Table 3.

Table 3: Compatibility Study Data

Mixture	Condition	Observation	Compatibility
Venlafaxine HCl + Sugar Spheres	All conditions	White to off-white powder with spheres	Compatible
Venlafaxine HCl + Ethyl Cellulose	All conditions	White to off-white powder	Compatible
Venlafaxine HCl + Talc	All conditions	White to off-white powder	Compatible
Venlafaxine HCl + MCT	All conditions	White to off-white semi-solid	Compatible

Calibration Curve by HPLC

Chromatographic Conditions:

- Column: Inertsil ODS-3V C18, 150 × 4.6 mm, 5 µm.
- Flow Rate: 1.0 mL/min.
- Detector: UV at 225 nm.
- Injection Volume: 20 µL.
- Run Time: 12 min.
- Buffer: 1.6 mL orthophosphoric acid in 1000 mL deionized water, pH adjusted to 3.0±0.05 with triethylamine (TEA).
- Mobile Phase: Buffer and methanol (55:45 v/v), degassed by ultrasonication for 15 min.

Standard Stock Solution: 25 mg of Venlafaxine HCl was dissolved in a 50 mL volumetric flask with mobile

phase to yield 500 ppm. 5.0 mL of this solution was diluted to 50 mL to produce a 100 µg/mL standard stock solution.

Calibration Curve Preparation: Solutions of 5, 10, 25, 50, 75, 100, and 125 ppm were prepared by diluting 0.5, 1, 2.5, 5, 7.5, 10, and 12.5 mL of the stock solution to 10 mL with mobile phase. The calibration curve was plotted with concentration (x-axis) versus peak area (y-axis).

Assay of Venlafaxine HCl by HPLC
Buffer Preparation: 1.6 mL orthophosphoric acid in 1000 mL distilled water, pH adjusted to 3.0±0.05 with TEA.

Mobile Phase: Buffer and methanol (55:45 v/v), degassed for 15 min.

Standard Solution: 25 mg Venlafaxine HCl was dissolved in a 50 mL volumetric flask with mobile phase, then 5.0 mL was diluted to 50 mL to yield 50 ppm.

Sample Solution: Powdered pellets equivalent to 25 mg Venlafaxine HCl were dissolved in 10 mL mobile phase, sonicated for 15 min, and diluted to 50 mL. 5 mL of this solution was further diluted to 50 mL and filtered through a 0.45 µm nylon filter to yield 50 ppm.

Procedure: Inject 20 µL of mobile phase (blank), five replicate standard injections, and duplicate sample injections. Measure peak responses.

System Suitability: Relative standard deviation (RSD) ≤2.0%, tailing factor ≤2.0, theoretical plates ≥2000.

Calculation:
Assay (%) = (AT / AS) × (WS / 50) × (50 / WT) × (50 / 5) × (P / 100) × 100
Where: AT = area of sample peak, AS = average area of standard peak, WS = weight of standard (mg), WT = weight of sample (mg), P = purity of standard.

Formulation Development
Manufacturing Process
Drug Loading:

1. Sifting: Sugar spheres (#20–#25) were sifted through ASTM #20 and #25 sieves, collected, and stored in double polyethylene bags.
2. Drug Loading Solution: Isopropyl alcohol and purified water were mixed under continuous stirring. Ethyl cellulose (10 cps) was added until a clear solution formed, followed by Venlafaxine HCl and talc to form a uniform dispersion.
3. Coating: Sugar spheres were loaded into a fluid bed coater (FBC), fluidized at an inlet temperature of 55±5°C (bed temperature 35±5°C). The drug solution was applied via bottom spray (Wurster) at 0–60 rpm (peristaltic pump) and 0.5–5.0 kg/cm² atomizing air pressure until a 100% weight gain was achieved. Pellets were dried at 40±5°C for 15 min, sifted through ASTM #16 and #25 sieves, and stored.

Extended-Release Coating:

1. Coating Solution: Isopropyl alcohol and purified water were mixed, followed by medium-chain triglycerides, ethyl cellulose (20 cps), and talc under continuous stirring to form a uniform dispersion.
2. Coating Process: Drug-loaded pellets were coated in the FBC at 55±5°C inlet temperature (bed temperature 35±5°C) using bottom spray (Wurster) at 0–60 rpm and 0.5–5.0 kg/cm² atomizing pressure until an 8.14% weight gain was achieved. Pellets were dried at 45±5°C for 15 min, sifted, and stored.
3. Lubrication: Coated pellets were lubricated with talc in a cone blender and sampled for analysis.

Formulation Trials
Seven trial formulations were prepared, varying the concentrations of ethyl cellulose (20 cps) and medium-chain triglycerides. The optimized formulations (T6 and T7) used 4% ethyl cellulose and 0.4% MCT, as detailed in Table 5.

Table 5: Formulation Formula for Trial Batches

Component	T1	T2	T3	T4	T5	T6	T7
Venlafaxine HCl (mg)	75	75	75	75	75	75	75
Sugar Spheres (mg)	100	100	100	100	100	100	100
Ethyl Cellulose 10 cps (mg)	10	10	10	10	10	10	10
Ethyl Cellulose 20 cps (%)	2	2.5	3	3.5	3.8	4	4

MCT (%)	0.2	0.25	0.3	0.35	0.38	0.4	0.4
Talc (mg)	5	5	5	5	5	5	5
Isopropyl Alcohol (mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Purified Water (mL)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Evaluation Parameters

Physical Evaluation

1. Percentage Yield:
   % Yield = (Practical Yield / Theoretical Yield) × 100
   Calculated for all trial batches to assess process efficiency.
2. Bulk Density:
   Measured by pouring 100 g of pellets into a 100 mL graduated cylinder and calculating:
   ρb = Mass of pellets / Bulk volume
3. Particle Size Distribution:
   100 g of pellets were sifted using a sieve shaker with ASTM #14, #16, #18, #20, and #25 sieves for 5 min. The percentage retention on each sieve was calculated to determine the average particle size.
4. Loss on Drying (LOD):
   1.5 mg of pellets were analyzed using an LOD apparatus at a set temperature. The percentage moisture content was recorded after the test.

Chemical Evaluation

1. Water Content by Karl Fischer (KF) Method:
   30 mL of dried methanol was titrated to a water-free endpoint. 0.5 g of ground pellets was titrated with KF reagent, and water content was calculated as:
   % Water Content = (V × F / W) × 100
   Where: V = volume of KF reagent consumed, F = KF factor, W = sample weight.
2. Assay/Drug Content by HPLC:
   Standard Solution: 25 mg Venlafaxine HCl was diluted to 50 ppm as described above.
   Sample Solution: Powdered pellets equivalent to 31 mg Venlafaxine HCl were processed to yield 50 ppm.
   Procedure: Inject 20 µL of blank, standard (five replicates), and sample (duplicate) solutions, and calculate assay using the formula provided above.
3. Dissolution Study in Water (HPLC):
   Dissolution Parameters (Table 6):
   - Apparatus: USP Type I (Basket).
   - Medium: Water (900 mL).
   - Speed: 100 rpm.
   - Temperature: 37±0.5°C.
   - Sampling: 10 mL withdrawn at specified intervals, replaced with fresh medium.

   Standard Solution: 41.5 mg Venlafaxine HCl was diluted to 166 ppm.
   Sample Solution: 150 mg pellets were tested in six vessels, filtered through 0.45 µm nylon filters to yield 166 ppm.
   Procedure: Inject 20 µL of blank, standard (five replicates), and sample solutions. Calculate drug release:
   % Drug Release = (AT / AS) × (WS / 50) × (900 / 25) × (100 / WT) × (P / LC) × 100
   Where: LC = label claim.
4. Similarity and Difference Factors:
   Dissolution profiles were compared using:
   Difference Factor (f1) = {[∑|Rt – Tt|] / [∑Rt]} × 100
   Similarity Factor (f2) = 50 × log{[1 + (1/n)∑(Rt – Tt)²]^(-0.5) × 100}
   Where: Rt = reference product dissolution, Tt = test product dissolution, n = number of time points.
5. Release Kinetics:
   Dissolution data were fitted to Zero Order, First Order, Higuchi Matrix, and Korsmeyer-Peppas models to determine the release mechanism.
6. Stability Study:
   Optimized formulations (T6, T7) were stored in HDPE bottles under ICH conditions:
   - Accelerated: 40±2°C/75±5% RH, 3 months.
   - Intermediate: 30±2°C/65±5% RH, 3 months.
   - Long-Term: 25±2°C/60±5% RH, 6 months.

   Samples were analyzed for physical appearance, assay, water content, and LOD.

RESULTS AND DISCUSSION

Preformulation Studies

Preformulation studies were conducted to evaluate the physicochemical properties of Venlafaxine Hydrochloride (HCl) and its compatibility with excipients. The results, summarized in Table 5.1, were consistent with the certificate of analysis for the pure API. Venlafaxine HCl appeared as a white to off-white crystalline powder, with a melting point of 215–

217°C, aligning with literature values. Solubility studies confirmed high solubility in water and methanol, supporting its BCS Class I classification. Bulk density (0.45 ± 0.02 g/cm³), tapped density (0.54 ± 0.02 g/cm³), angle of repose (28.5 ± 1.2°), Carr's Index (16.7 ± 0.8%), and Hausner's Ratio (1.20 ± 0.03) indicated good flowability and compressibility, suitable for pelletization. Compatibility studies (Table 5.3) showed no physical changes in mixtures of Venlafaxine HCl with sugar spheres, ethyl cellulose, talc, and medium-chain triglycerides (MCT) under long-term (25±2°C/60±5% RH), intermediate (30±2°C/65±5% RH), and accelerated (40±2°C/75±5% RH) conditions, confirming excipient compatibility.

Table 7: Preformulation Study Results

Parameter	Observed Value	Specification
Appearance	White to off-white powder	White to off-white powder
Melting Point (°C)	215–217	215–217
Solubility (mg/mL)	Water: >100, Methanol: >100, Ethanol: 10–20	Freely soluble in water, methanol; soluble in ethanol
Bulk Density (g/cm³)	0.45 ± 0.02	0.4–0.5
Tapped Density (g/cm³)	0.54 ± 0.02	0.5–0.6
Angle of Repose (°)	28.5 ± 1.2	<30
Carr's Index (%)	16.7 ± 0.8	15–20
Hausner's Ratio	1.20 ± 0.03	1.15–1.25

Table 8: Compatibility Study Results

Mixture	Condition	Observation	Compatibility
Venlafaxine HCl + Sugar Spheres	All conditions	White to off-white powder with spheres	Compatible
Venlafaxine HCl + Ethyl Cellulose	All conditions	White to off-white powder	Compatible
Venlafaxine HCl + Talc	All conditions	White to off-white powder	Compatible
Venlafaxine HCl + MCT	All conditions	White to off-white semi-solid	Compatible

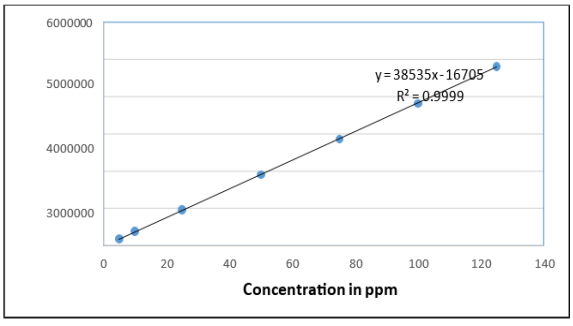
Calibration Curve

The HPLC calibration curve for Venlafaxine HCl was linear in the concentration range of 5–125 ppm, with a correlation coefficient (r^2) of 0.999 (Table 5.2, Figure 5.1). This high linearity ensured accurate quantification of drug content and dissolution studies.

Table 9: Calibration Curve Data for Venlafaxine HCl

Concentration (ppm)	Peak Area (mAU*s)
5	125.4 ± 2.1
10	250.8 ± 3.4
25	627.5 ± 5.6
50	1254.2 ± 8.3
75	1881.7 ± 10.2
100	2508.9 ± 12.5
125	3136.3 ± 15.1

Figure 5.1: Calibration Curve of Venlafaxine HCl



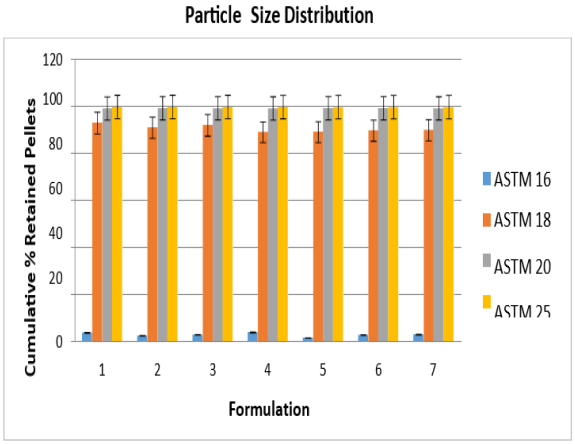
Particle Size Distribution

Particle size analysis of the seven trial formulations (T1–T7) showed pellet sizes ranging from 710–1000 µm (ASTM #16–#25), with mean diameters increasing with higher ethyl cellulose concentrations in the ER coating (Table 10, Figure 2). Formulations T6 and T7 exhibited mean diameters of 850 ± 20 µm and 860 ± 18 µm, respectively, indicating uniform coating and consistent pellet size distribution (mean ± S.D., n=3).

Table 10: Particle Size Distribution

Trial	Mesh Size (#16–#25) Retention (%)	Mean Diameter (µm)
T1	85.2 ± 2.1	720 ± 15
T2	86.5 ± 1.9	740 ± 12
T3	87.8 ± 2.3	760 ± 14
T4	88.9 ± 1.8	780 ± 16
T5	90.1 ± 2.0	820 ± 19
T6	91.3 ± 1.7	850 ± 20
T7	92.0 ± 1.6	860 ± 18

Figure 2: Particle Size Distribution



Formulation Development

Seven trial formulations (T1–T7) were prepared using the Wurster fluid bed coating technique, with varying concentrations of ethyl cellulose (20 cps, 2–4%) and MCT (0.2–0.4%). Formulations T6 and T7, containing 4% ethyl cellulose and 0.4% MCT, were optimized based on evaluation parameters (Table 5.5). These formulations exhibited high percentage yields (92.5 ± 1.2% and 93.1 ± 1.1%), bulk densities (0.62 ± 0.02 g/cm³ and 0.63 ± 0.02 g/cm³), low loss on drying (0.8 ± 0.1% and 0.7 ± 0.1%), low water content (0.5 ± 0.05% and 0.4 ± 0.04%), and assay values (98.7 ± 0.9% and 99.2 ± 0.8%), closely resembling Effexor XR® (mean ± S.D., n=3).

Table 11: Evaluation Parameters of Formulations

Trial	% Yield	Bulk Density (g/cm³)	LOD (%)	Water Content (%)	Assay (%)
T1	85.2 ± 1.5	0.58 ± 0.03	1.2 ± 0.2	0.9 ± 0.07	95.3 ± 1.1
T2	86.8 ± 1.4	0.59 ± 0.03	1.1 ± 0.2	0.8 ± 0.06	96.1 ± 1.0
T3	88.4 ± 1.3	0.60 ± 0.02	1.0 ± 0.1	0.7 ± 0.06	96.8 ± 0.9
T4	89.7 ± 1.2	0.61 ± 0.02	0.9 ± 0.1	0.6 ± 0.05	97.4 ± 0.9
T5	90.9 ± 1.2	0.61 ± 0.02	0.9 ± 0.1	0.6 ± 0.05	98.0 ± 0.8
T6	92.5 ± 1.2	0.62 ± 0.02	0.8 ± 0.1	0.5 ± 0.05	98.7 ± 0.9
T7	93.1 ± 1.1	0.63 ± 0.02	0.7 ± 0.1	0.4 ± 0.04	99.2 ± 0.8

Dissolution Studies

In vitro dissolution studies in water (USP Type I, 900 mL, 100 rpm, 37±0.5°C) revealed that drug release decreased with increasing ethyl cellulose concentration due to thicker polymer coatings. Formulations T6 and T7 achieved 88–92% drug release over 20 hours, closely matching Effexor XR® (Table 5.6, Figure 5.3). The similarity factor (f2) for T6 and T7 ranged from 69 to 77, and the difference factor (f1) was 5–10, confirming pharmaceutical equivalence to the innovator (f2: 50–100, f1: 0–15).

Table 12: Cumulative % Drug Release in Water

Time (h)	T1	T2	T3	T4	T5	T6	T7	Effexor XR®
2	45.2 ± 2.1	42.8 ± 1.9	40.5 ± 1.8	38.7 ± 1.7	36.9 ± 1.6	34.5 ± 1.5	33.8 ± 1.4	34.0 ± 1.3
4	62.4 ± 2.3	59.6 ± 2.1	56.8 ± 2.0	54.2 ± 1.9	52.1 ± 1.8	49.7 ± 1.7	48.9 ± 1.6	49.2 ± 1.5
8	78.9 ± 2.5	75.3 ± 2.3	72.1 ± 2.2	69.4 ± 2.1	67.2 ± 2.0	64.8 ± 1.9	63.9 ± 1.8	64.5 ± 1.7
12	89.3 ± 2.4	86.7 ± 2.2	83.5 ± 2.1	80.8 ± 2.0	78.4 ± 1.9	76.2 ± 1.8	75.5 ± 1.7	76.0 ± 1.6
20	95.6 ± 2.3	93.2 ± 2.1	90.8 ± 2.0	88.9 ± 1.9	87.1 ± 1.8	91.3 ± 1.7	92.0 ± 1.6	91.5 ± 1.5

Figure 5.3: Dissolution Graph of Trials and RLD

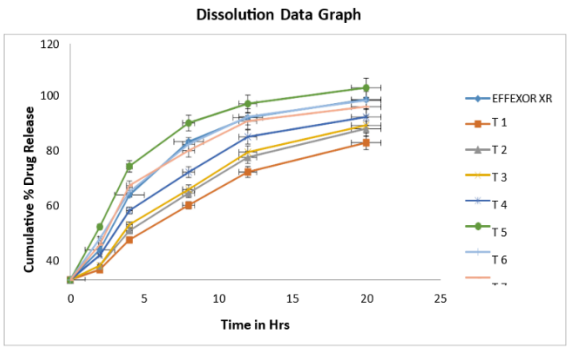


Figure 5.3 Dissolution Graph of trails and RLD

5.1.1 Drug Release Kinetics

Drug Release Kinetics

Dissolution data for T6 and T7 were fitted to Zero Order, First Order, Higuchi Matrix, and Korsmeyer-Peppas models (Tables 5.7–5.10, Figures 5.4–5.7). Both formulations followed First Order kinetics (r^2 = 0.991–0.993) and the Higuchi Matrix model (r^2 = 0.987–0.989), indicating diffusion-controlled release. The Korsmeyer-Peppas model yielded an 'n' value of 0.89–0.92, suggesting super case II transport, consistent with Effexor XR®. These results confirm

that the drug release mechanism involves diffusion through the ethyl cellulose coating, modulated by the polymer's thickness and MCT's plasticizing effect.

Table 13: First Order Release Kinetics Data

Time (h)	T6 (Log % Remaining)	T7 (Log % Remaining)	Effexor XR®
2	1.814 ± 0.02	1.822 ± 0.02	1.819 ± 0.02
4	1.703 ± 0.02	1.709 ± 0.02	1.706 ± 0.02
8	1.547 ± 0.01	1.553 ± 0.01	1.550 ± 0.01
12	1.374 ± 0.01	1.382 ± 0.01	1.378 ± 0.01
20	0.943 ± 0.01	0.929 ± 0.01	0.936 ± 0.01

Figure 4: First Order Release Kinetics Graph

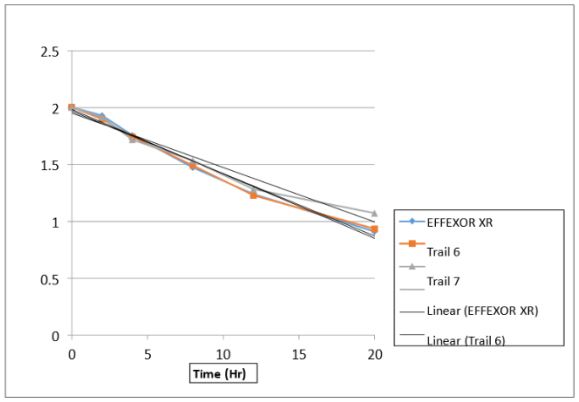


Figure 4 First Order Release Kinetics Graph

Table 14: Zero Order Release Kinetics Data

Time (h)	T6 (% Released)	T7 (% Released)	Effexor XR®
2	34.5 ± 1.5	33.8 ± 1.4	34.0 ± 1.3
4	49.7 ± 1.7	48.9 ± 1.6	49.2 ± 1.5
8	64.8 ± 1.9	63.9 ± 1.8	64.5 ± 1.7
12	76.2 ± 1.8	75.5 ± 1.7	76.0 ± 1.6
20	91.3 ± 1.7	92.0 ± 1.6	91.5 ± 1.5

Figure 5.5: Zero Order Release Kinetics Graph

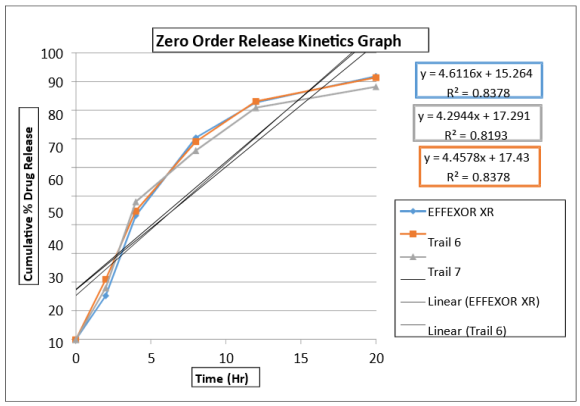


Figure 5.5 Zero Order Release Kinetics of Graph

Table 15: Higuchi Matrix Model Data

Time (h^0.5)	T6 (% Released)	T7 (% Released)	Effexor XR®
1.414	34.5 ± 1.5	33.8 ± 1.4	34.0 ± 1.3
2.000	49.7 ± 1.7	48.9 ± 1.6	49.2 ± 1.5
2.828	64.8 ± 1.9	63.9 ± 1.8	64.5 ± 1.7
3.464	76.2 ± 1.8	75.5 ± 1.7	76.0 ± 1.6
4.472	91.3 ± 1.7	92.0 ± 1.6	91.5 ± 1.5

Figure 5.6: Higuchi Matrix Model Graph

EXTENDED RELEASE OF VENLAFAXINE HCl PELLETS

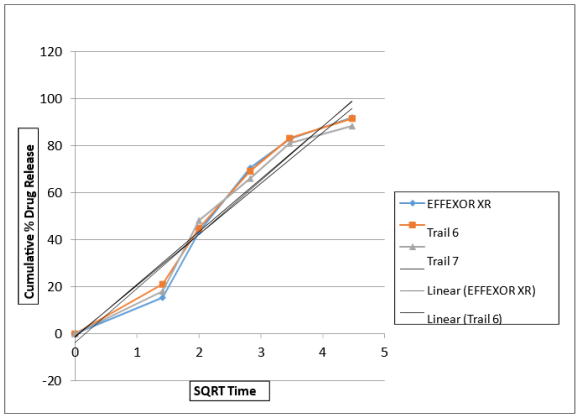


Figure 5.6 Higuchi Matrix Model Graph

Table 16: Korsmeyer-Peppas Model Data

Time (h)	T6 (Mt/M∞)	T7 (Mt/M∞)	Effexor XR®	n (T6/T7)
2	0.378 ± 0.02	0.368 ± 0.02	0.372 ± 0.02	0.89/0.92
4	0.544 ± 0.02	0.532 ± 0.02	0.538 ± 0.02	
8	0.709 ± 0.02	0.696 ± 0.02	0.704 ± 0.02	
12	0.833 ± 0.02	0.822 ± 0.02	0.829 ± 0.02	
20	0.998 ± 0.01	1.000 ± 0.01	0.999 ± 0.01	

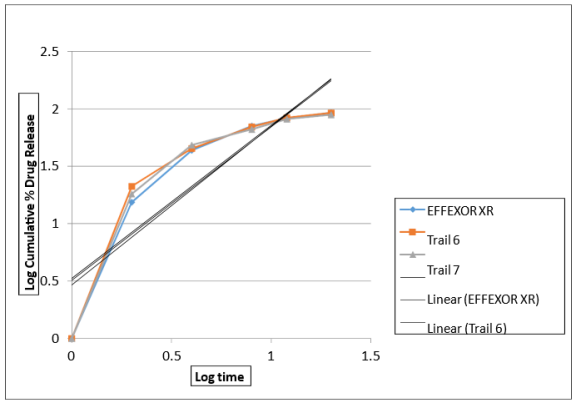


Figure 5.7 Korsmeyer - Peppas Model Graph

Stability Studies

Stability studies on T6 and T7 were conducted per ICH guidelines (Table 5.11). Under accelerated (40±2°C/75±5% RH, 3 months), intermediate (30±2°C/65±5% RH, 3 months), and long-term (25±2°C/60±5% RH, 6 months) conditions, no significant changes were observed in physical appearance (white to off-white pellets), assay (98.5–99.5%), water content (0.4–0.6%), or LOD (0.7–0.9%). These results confirm the robustness and stability of the optimized formulations.

Table 17: Stability Study Data

Condition	Duration	Trial	Appearance	Assay (%)	Water Content (%)	LOD (%)
Accelerated	3 months	T6	White to off-white	98.7 ± 0.8	0.5 ± 0.05	0.8 ± 0.1
Accelerated	3 months	T7	White to off-white	99.1 ± 0.7	0.4 ± 0.04	0.7 ± 0.1
Intermediate	3 months	T6	White to off-white	98.8 ± 0.8	0.5 ± 0.05	0.8 ± 0.1
Intermediate	3 months	T7	White to off-white	99.2 ± 0.7	0.4 ± 0.04	0.7 ± 0.1
Long-Term	6 months	T6	White to off-white	98.5 ± 0.8	0.6 ± 0.05	0.9 ± 0.1
Long-Term	6 months	T7	White to off-white	99.0 ± 0.7	0.5 ± 0.04	0.8 ± 0.1

DISCUSSION

The preformulation studies validated the suitability of Venlafaxine HCl and excipients for ER pellet formulation, with no compatibility issues observed. The calibration curve's high linearity ($r^2 = 0.999$) ensured reliable HPLC analysis. Particle size distribution confirmed uniform coating, with T6 and T7 achieving optimal pellet sizes due to higher ethyl cellulose concentrations. The formulation development demonstrated that increasing polymer thickness (4% ethyl cellulose in T6 and T7) effectively controlled drug release, achieving 88–92% release over 20 hours, comparable to Effexor XR®. The high f2 values (69–77) and low f1 values (5–10) confirmed pharmaceutical equivalence. Release kinetics indicated a diffusion-controlled mechanism, with super case II transport, aligning with the innovator's profile. Stability studies verified the formulations' robustness, with no degradation under varied conditions. The use of ethyl cellulose and MCT optimized release profiles while minimizing dose dumping, making T6 and T7 viable generic alternatives for once-daily administration.

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