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DESIGN AND DEVELOPMENT OF VENLAFLAXIN HCL EXTENDED RELEASE PELLETS THROUGH FBC

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ABSTRACT

Aim and Objective: Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption and onset of accompanying pharmacodynamic effects. The term modified release drug product is used to describe that alter the timing and or the rate of release of the drug substances. The objective of the present study was to formulate and evaluate the sustained release matrix tablet of venlafaxine hydrochloride.

Methods: Venlafaxine hydrochloride is a structurally novel antidepressant for oral administration. It is widely prescribed for the treatment of depression, generalized anxiety disorder, and social anxiety disorder. Venlafaxine hydrochloride is currently available as immediate release tablet and as an extended release capsules under the brand names of Effexor (WYETH AYERST) and Effexor XR (WYETH AYERST). The biological half-life of venlafaxine very short (5 h) and the dose is to be taken 2–3 times a day and the recommended maximum daily dose is 75–450 mg/day.

Results: Venlafaxine hydrochloride is an antidepressant and so it is to be taken for quite a long period. Hence, to reduce the dosing frequency, simple, lower cost sustained release tablets of venlafaxine were preferred for the development.

1.1 CONTROLLED DRUG DELIVERY SYSTEM

The realm of pharmaceuticals, oral drug delivery systems are broadly categorized into immediate release, novel drug delivery systems**,** modified release. Immediate release formulations, like tablets and capsules, are designed to release active ingredient promptly after oral intake of patient . On other hand, modified release products alter timing or rate of release to achieve therapeutic goals not attainable with conventional dosage forms.

Modified release dosage forms are classified as various types, including controlled release, extended-release, sustained-release, prolonged release, delayed-release, and targeted-release systems. Formulations aim to optimize oral bioavailability and concentration drug profile in blood, , particularly those falling under BCS (Biopharmaceutics Classification System) Class I.

In essence, modified release (extended release) technologies provide a strategic approach to enhance drug efficacy by controlling the release characteristics, such as time course and location, in a manner that conventional dosage forms like ointments, solutions and rapidly dissolving forms cannot achieve. This optimization contributes to improved therapeutic outcomes and patient convenience.

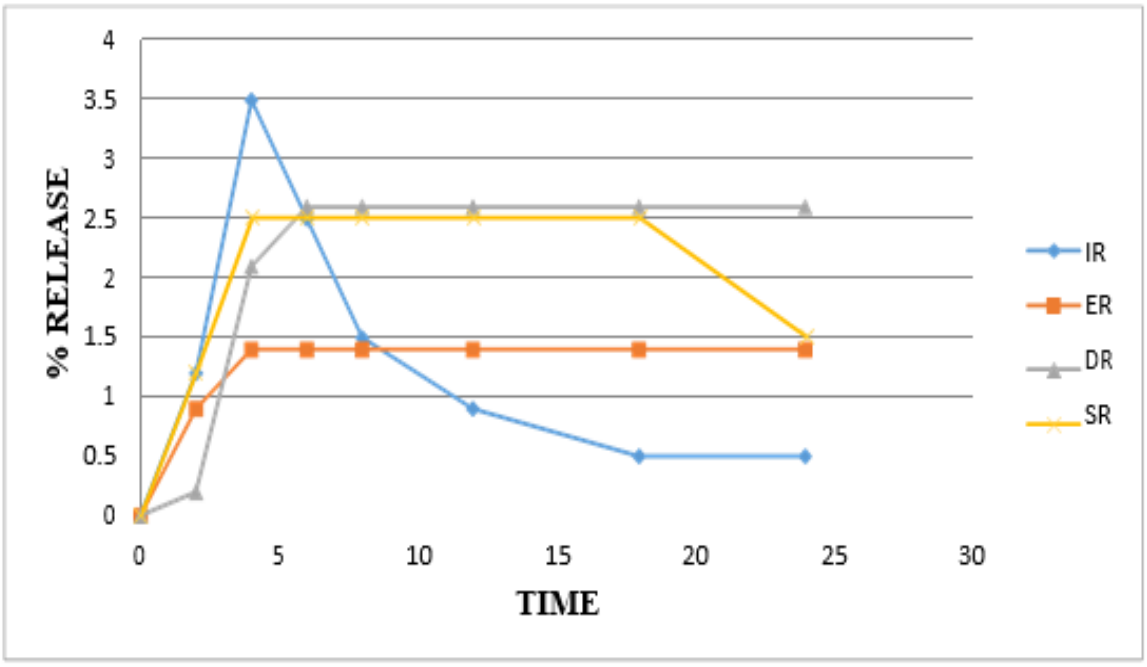


Figure 1.1 Release of Solid Oral Dosage Form.

The extended-release formulation of Venlafaxine HCl pellets aims to enhance absorption rates and maintain consistent in-vitro drug release. However, a drawback encountered is the occurrence of dose dumping. Venlafaxine, classified as a BCS-I drug with a relatively low bioavailability of 42±5%, is susceptible to uncontrolled in-vitro drug release, leading to dose dumping. Dose dumping refers to the premature and exaggerated release of a drug in the body due to environmental factors, resulting in adverse effects.

To address the issue of dose dumping, optimization of the extended-release formulation was carried out. This involved the utilization of various polymers at different concentrations to create an enteric coating. This coating serves as a protective layer to regulate drug release. The extended-release formulation of Venlafaxine HCl was achieved through the pelletization technique.

1.2 PELLETIZATION

Pelletization is a agglomeration process transforms granules or fine powders to free-flowing, spherical units known as pellets.

Pellets are freely flowing, small spherical particles formed through agglomeration of fine powders or spherical particles containing active pharmaceutical ingredients (API) and excipients. Ranging in size from 500 to 1500μm (as depicted in Figure No. 1.2), pellets offer flexibility in formulation development and confer therapeutic advantages to patients.

These pellets are encapsulated in gelatin capsules(hard) or compressed to tablets, specifically disintegrating tablets that break into multiple units upon administration. The multiparticulate nature of pellets, along with granules, microcapsules, and beads, presents both pharmacological and technological benefits compared to traditional single-unit solid dosage forms. This concept was emerged in 1950s.

When ingested orally, multiparticulate dosage forms disperse freely in the tract of gastrointestinal system , maximizing absorption of drug while minimizing irritation at mucosa caused by the certain irritating drugs. This characteristic helps reduce both inter and intra-patient variability. Pellets allow for easy division into desired dose strengths without altering the formulation or manufacturing process. Moreover, they enable the achievement of required release profiles at the different or same sites within GI tract.

1.2.1 Advantages

- When used in modified release formulations, pellets demonstrate a lower risk of dose dumping compared to single-unit reservoir-type formulations.
- Pellets are particularly recommended for individuals facing challenges in swallowing or experiencing dysphagia, such as children and the elderly.
- Pelletization plays a role in reducing both intra and intersubject variability in plasma by minimizing variations in gastric emptying rates and overall transit times.
- The pelletization process generates spheroids having high loading capacity of the active drug, avoiding the production of excessively large particles.

1.2.3 Disadvantages

- Filling pellets into capsules can lead to increased costs associated with capsule filling.
- Tableting of pellets can result in the destruction of the film coating applied to the pellets.

- The size of pellets may differ from one formulation to another but typically falls within the range of 0.05 mm to 2 mm.
- Managing the manufacturing process is challenging due to a multitude of process variables and formulation variables.

1.2.4 Properties of Pellets

- Uncoated pellets should possess consistent spherical size, excellent flow characteristics, minimal dust formation, reliable packing, easy coating, and a uniform surface.
- For coated pellets, it is essential to retain all the aforementioned properties while also achieving desirable drug release characteristics.

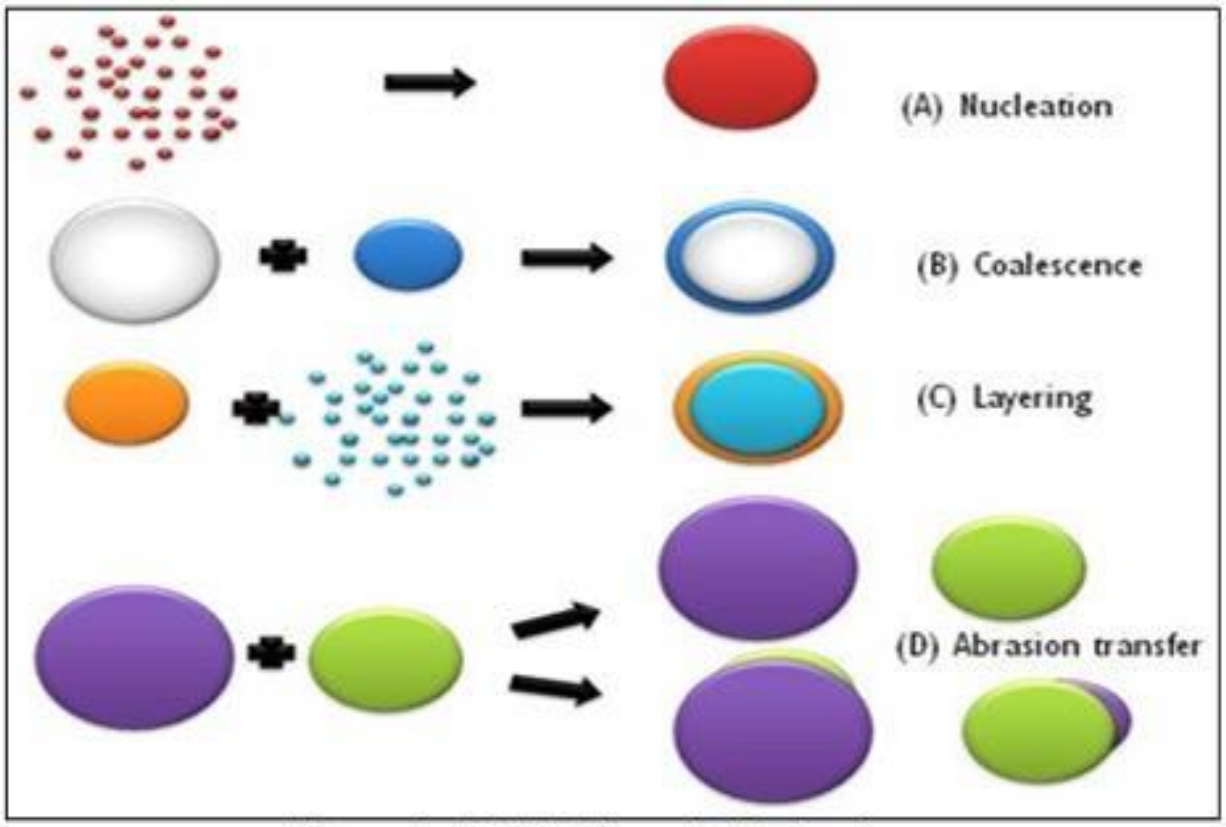


Figure 1.3 Pellet Growth Mechanism.

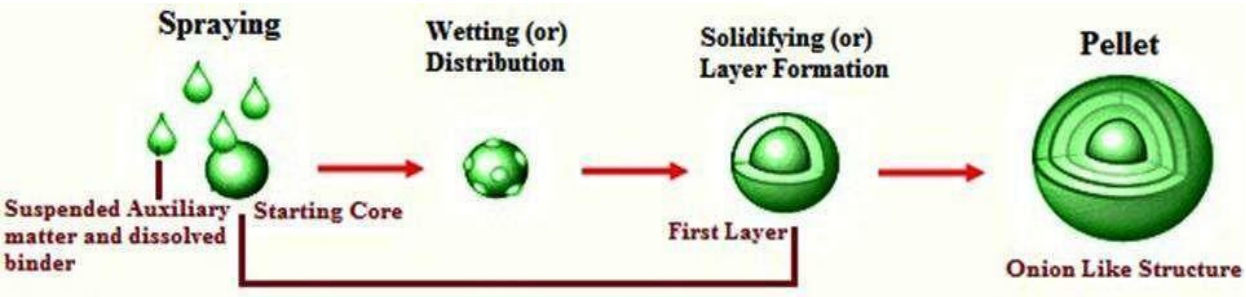


Figure 1.7 Solution/Suspension Layering Technique

2.1 METHODOLOGY

2.1.2 Preformulation studies

Appearance of the Venlafaxine HCl was white to off white color powder, done by visual observation. 4.3.1.2 Melting Point As per literature review/ certificate of analysis of the Venlafaxine HCl melting point range is 215 to 217°C.

2.1.3 Solubility

Solubility determined by saturation shake flask method. Amount of drug was added to 1ml solvent in excess and stirred for 74h. later the system was vortexed, centrifuged at 6000rpm to sediment undissolved part and then the supernatant was filtered using 0.22um Millipore filter. Finally the obtained filtrated was used for spectroscopic analysis using HPLC for determination of concentration.

2.1.4 Flow Properties

Flow properties of pellets are evaluated.

2.1.5 Compatibility Study

Venlafaxine HCl was blended with excipients in equal ratio and subjected for long term, Intermediate and Accelerated conditions (closed) to study any changes in their physical properties. The quantities of the excipients were selected is show in the table.

Table 4.3 Compatibility Study Data

S.No.	Ingredients	Ratio	Physical Appearance	25°C + 60%RH & 40°C + 75% RH		
				7 D	15 D	30 D
1	Venlafaxine HCl (API)	1	#	√	√	√
2	API + Sugar spheres (#20-#25)	1:2	!	√	√	√
3	API + Ethyl cellulose (10 cps)	1:0.5	#	√	√	√
4	API + Ethyl cellulose (20 cps)	1:0.5	#	√	√	√

5	API + Medium-chain triglycerides	1:0.2	$	√	√	√
6	API + Talc	1:0.2	#	√	√	√
7	API + All above excipients + Water + Isopropyl alcohol	1:2:0.5:0.5:0.2:0.2	$	√	√	√
8	All above excipients + Water + Isopropyl alcohol	2:0.5:0.5:0.2:0.2	$	√	√	√

Note: - #= White to off white powder != White to off white powder with spheres $= White to off white semi-solid √=Compatible

2.1.6 Determination of Calibration Curve by HPLC

Chromatographic Conditions:

Column: Inertsil ODS-3V C18, 150×4.6mm, 5µm an equivalent.

Flow Rate: 1.0ml/min.

Detector: UV

Wavelength : 225nm

Injection Volume: 20µL

Run Time: 12 minutes

Buffer Preparation:

Prepare a buffer solution by combining 1.6 ml of OPA with 1000 ml of deionized water (DM water) and adjusting to pH 3.0±0.05 using triethylamine (TEA).

Mobile Phase:

Create the mobile phase by mixing the buffer solution and methanol in a volumetric flask in a ratio of 55:45. Ensure the mixture is degassed through ultrasonication for 15 minutes.

Preparation of Standard Stock Solution :

weigh 25 mg of Venlafaxine HCl, transfer it to a volumetric flask of 50ml, and dilute with mobile phase to make up to the mark, resulting in a concentration of 500 ppm. Take 5.0 ml of this solution (500 ppm), transfer it to another volumetric flask of 50ml, dilute with mobile phase for volume makeup, and then mix for producing a standard stock solution with concentration of 100 µg/ml.

Preparation of Calibration Curve Solution:

Dilute 0.5 ml of stock solution to 10ml with the mobile phase, yielding a 5 ppm solution. From the standard stock solution, use 0.5, 1, 2.5, 5, 7.5, 10, and 12.5 ml, dilute each to 10 ml with the mobile phase, and create solutions with concentrations of 5, 10, 25, 50, 75, 100, and 125 ppm, respectively. Construct the calibration curve using these solutions, by placing concentration on x-axis and peak area on y-axis.

2.1.7 Assay of Venlafaxine HCl (API) By HPLC Method

Buffer Preparation: Mix 1.6 ml of orthophosphoric acid to1000 ml of distilled water and adjust pH to 3.0±0.05 using triethylamine.

Mobile Phase Preparation: Combine buffer solution and methanol in a 55:45 ratio in a volumetric flask. Degass the mixture through ultrasonication for 15 minutes.

Preparation of Standard Solution: weigh 25 mg of Venlafaxine HCl WS, transfer to a 50 ml volumetric flask, dilute with mobile phase to fill the volume. Take 5.0 ml of this solution, transfer it to another 50 ml volumetric flask, dilute with the mobile phase to fill the volume, and mix. The final concentration is 50 ppm of Venlafaxine HCl.

Preparation of Sample Solution: Weigh the powder to about 25 mg of Venlafaxine HCl, transfer to a 50 ml volumetric flask. Add mobile phase of 10ml, sonicate for 15 minutes with intermittent shaking, make up the volume with mobile phase. Transfer 5 ml of solution to 50 ml volumetric flask, dilute the mobile phase to fill the volume, and then mix. Filter solution through a 0.45µm Nylon filter paper. The final concentration is 50 ppm of Venlafaxine HCl.

Procedure: Inject (20µL) of the mobile phase as a blank, 5 replicate injections of the standard solution, and a single preparation of the sample solution (duplicate injection) into chromatograph. Measure responses for major peak.

System Suitability Criteria:

The coefficient variation for 5repeated injections of standard solution should not exceed 2.0percent. The tailing factor of Venlafaxine HCL peak must not exceed 2.0. The theoretical plates for Venlafaxine HCL should not fall below 2000.

Table 4.4 Injection Sequence

S.No.	No. of Injections	Name of the sample
1	1	Blank
2	5	Standard solution
3	2	Sample solution
4	1	Bracketing standard

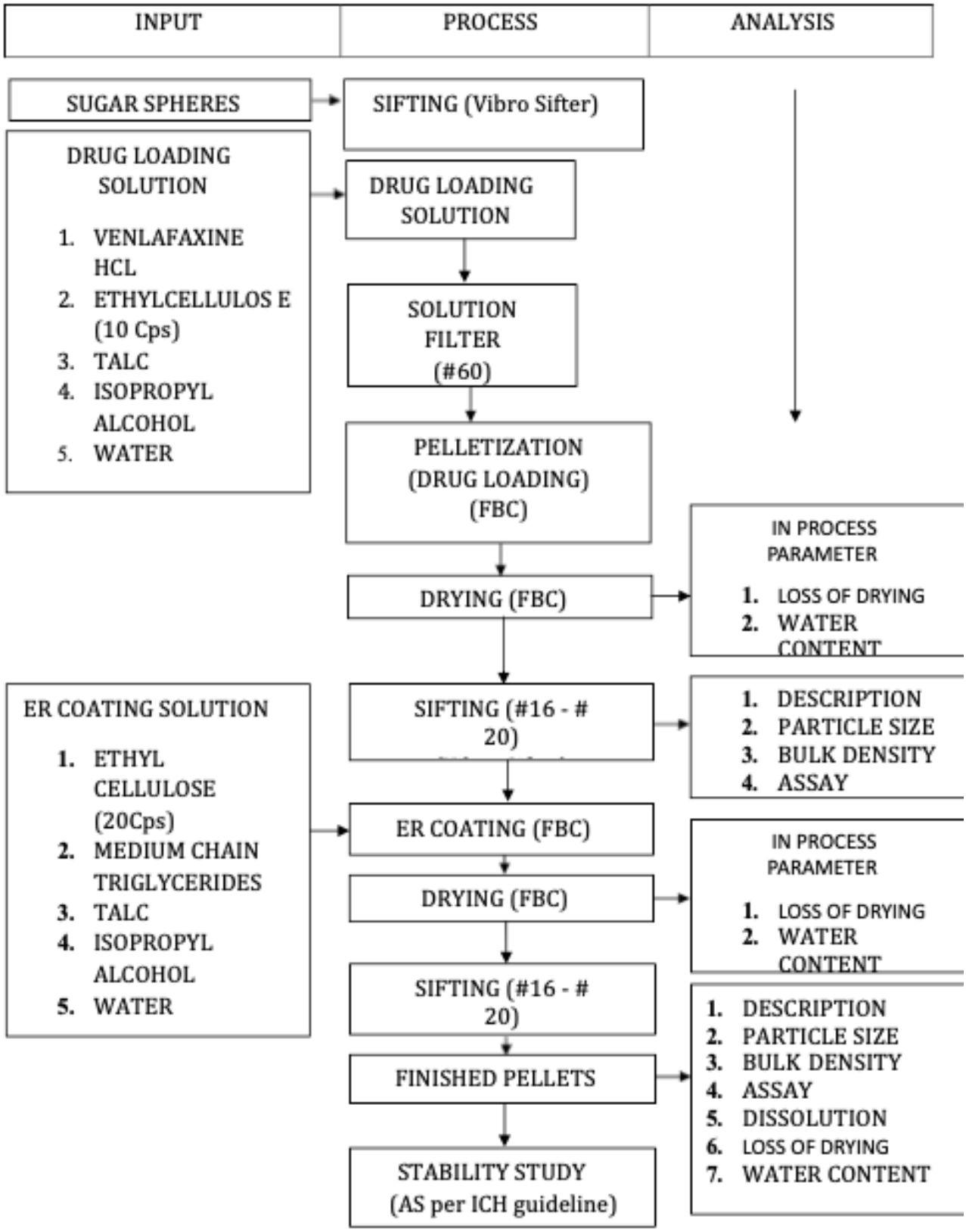
2.2 Formulation Development

After studying the patents on Venlafaxine HCl modified release pellets, a list of polymer, which can be used, was prepared which included various coating polymer like Ethyl cellulose and Medium-chain triglycerides. Feasibility trial was performed in order to load the drug in to the sugar sphere as describe

S.No.	Ingredients (in %)	Formulation						
		T 1	T 2	T 3	T 4	T 5	T 6	T 7
CORE								
1	Sugar Spheres (#20-#25)	52.9	54.9	55.9	57	59.2	58.1	58.1
DRUG LOADING								
2	Venlafaxine HCl	33	33	33	33	33	33	33
3	Ethyl Cellulose (10 cps)	5	3	2	2	2	2	2
4	Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5
5	Isopropyl Alcohol	Q. S	Q.S	Q.S	Q. S	Q.S	Q.S	Q.S
6	Purified Water	Q. S	Q.S	Q.S	Q.S	Q. S	Q.S	Q. S
EXETENDED RELEASE								
7	Ethyl Cellulose (20 cps)	6	6	6	5	3	4	4
8	Medium-chain triglycerides	0.6	0.6	0.6	0.5	0.3	0.4	0.4
9	Talc	1	1	1	1	1	1	1
10	Isopropyl Alcohol	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
11	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q. S
LUBRICATION								
12	Talc	1	1	1	1	1	1	1
	Total	100	100	100	100	100	100	100

Table 4.5 Formulation formula for trails batch

4.1.1.1 Manufacturing process



Formulation Procedure for Extended-Release Pellets

Drug Loading:

1. Sifting of Sugar Pellets: Sugar pellets (#20-#25) were sifted through ASTM #20 & #25, collecting passed and retained portions in separate double polyethylene bags.

2. Preparation of Drug Loading Solution: In a beaker, Isopropyl alcohol and purified water were dispensed and stirred continuously. Ethyl cellulose 10cps, Venlafaxine Hydrochloride, and Talc were added successively, stirring until a clear solution was obtained.

3. Loading Sugar Pellets into FBC: Sugar pellets (#20-#25) were loaded into the fluidized bed coater (FBC). The inlet temperature was set to 55±5°C, reaching a bed temperature of about 35±5°C. Coating was done using bottom spray Wurster with specified RPM and atomizing air pressure until the target weight gain of 100% was achieved. After drug loading, pellets were dried in the FBC for approximately 15 minutes at a bed temperature of about 40±5°C. The pellets were dried sifted through #16, collecting #25 retained and then passed the portions separately.

Extended-Release Coating:

1. Preparation of Coating Solution: Isopropyl alcohol and purified water were combined in a beaker, and within this hydroalcoholic solvent, medium chain triglycerides, Ethyl cellulose 20cps, and Talc were added successively and stirred until a clear solution was obtained.

2. Loading Drug-Loaded Pellets into FBC: Drug-loaded pellets were loaded into the FBC, and the process was similar to drug loading, with the inlet temperature set to 55±5°C, reaching a bed temperature of about 35±5°C. Coating was done using bottom spray Wurster until the target weight gain of 8.14% was achieved. After coating, the pellets were dried in the FBC for approximately 15 minutes at a bed temperature of about 45±5°C. The dried pellets were then sifted through #16, collecting #25 retained and passed portions separately. Recordings of various parameters were made every 30 minutes in a record book during both drug loading and coating stages.

2.2 EVALUATION PARAMETER

Physical Evaluation

Percentage (%) Yield

All batches of extended-release Venlafaxine hydrochloride pellets, produced using fluid bed coating, underwent assessment for the percentage yield of the pellets. The actual percentage yield was determined using the formula.

Bulk Density:

Apparent bulk density was determined by pouring blend to a graduated measuring cylinder (100ml). The bulk density was calculated using the formula:

Particle Size Distribution and Determination:

Pellets obtained after functional coating underwent sieving to check the average size. The pellets (100 gm) were sifted through a series of sieves (14 #, 16 #, 18#, 20 #, and 25 #). The % retention of pellets by each mesh was calculated, determining the average particle size.

Loss of Drying (LOD) Determination:

The LOD apparatus was used to determine the % moisture content. Pellets (1.5 mg) were placed on the LOD apparatus plate, and after the test, the % moisture content was recorded.

Water Content by KF Method:

The dried methanol was titrated with Karl Fischer reagent to make it water-free. About 0.5 g of sample was weighed, ground to fine powder, and titrated with Karl Fischer reagent. The % water content was calculated.

Assay/Drug Content (By HPLC Method):

Standard and sample solutions were prepared for HPLC analysis to determine the assay/drug content. The formula used for calculation:

Calculation

$$\text{Assay (\%)} = \frac{AT}{100} \times \frac{WS}{AS} \times \frac{5}{100} \times \frac{50}{50} \times \frac{P}{WT} \times \frac{}{5} \times$$

Dissolution Study in Water as Media (By HPLC Method):

The in vitro drug release from Venlafaxine hydrochloride extended-release pellets was evaluated using a Basket apparatus and HPLC.

Table 4.6 Dissolution parameter

Apparatus	Basket Apparatus (# 24)
Media	Purified water/Methanol
Volume	900 ml
RPM	100
Temperature	37°C

Similarity Factor and Difference Factor:

The dissolution profiles are analyzed using difference factor (f1) and similarity factor (f2), calculated to specific formulas.

Release Kinetics:

Various kinetic models, including Zero Order, First Order, Higuchi Matrix, and Krosmeyer Peppas, were applied in order to analyze the in vitro release data.

Stability Study:

Stability studies were conducted as per ICH guidelines to assess the impact of environmental factors on the quality of the pellets. The study included analysis at intervals for parameters such as assay of the active ingredient, known degradation products, disintegration time, dissolution time, and appearance. The pellets were packed into HDPE bottles for stability assessment.

Table 4.7 Storage conditions and duration of stability study.

Study	Storage condition	Duration
Long term	25 ± 2 °C/60± 5% RH	6 months
Intermediate	30 ± 2 °C/65± 5% RH	3 months
Accelerated	40 ± 2 °C/75± 5% RH	3 months

3. RESULT AND DISCUSSION

3.1 PREFORMULATION STUDY

The preformulation study of Venlafaxine HCl was carried out through various evaluation parameters with respect to the certificate of analysis of pure Venlafaxine HCl API after study the preformulation they carried to the formulation of extended release of pellets. The preformulation study results shows in above table no.5.1 which test results comes under the specification of certificate of analysis of pure API.

Table 5.1 Preformulation study

S.No.	TEST PARAMETER	RESULTS
1	Physical Appearances	White to off white color powder
2	Melting Point	214.5-218°C
3	Solubility	Freely soluble in water & methanol Practically insoluble in acetone.
4	Bulk Density	0.272 g/ml
5	Tapped Density	0.468g/ml
6	Carr's index	42.00 %
7	Hausner's ratio	1.724
8	Flow properties	Very-very poor flow
9	Assay	99.34

3.2 UV-Analysis

The concentration range of 5-125 ppm. r^2 value was found to be 0.999 indicates linearity.

Table 5.2 Calibration curve data of Venlafaxine HCl

Conc. (in ppm)	Peak area	Conc. Average (X-axis)	390
5	181275	Area Average (Y-axis)	14938235
10	385350	Slop (m)	38346
25	963174	Intercept (C)	-16705
50	1910248		
75	2863422		
100	3820196		
125	4814570		

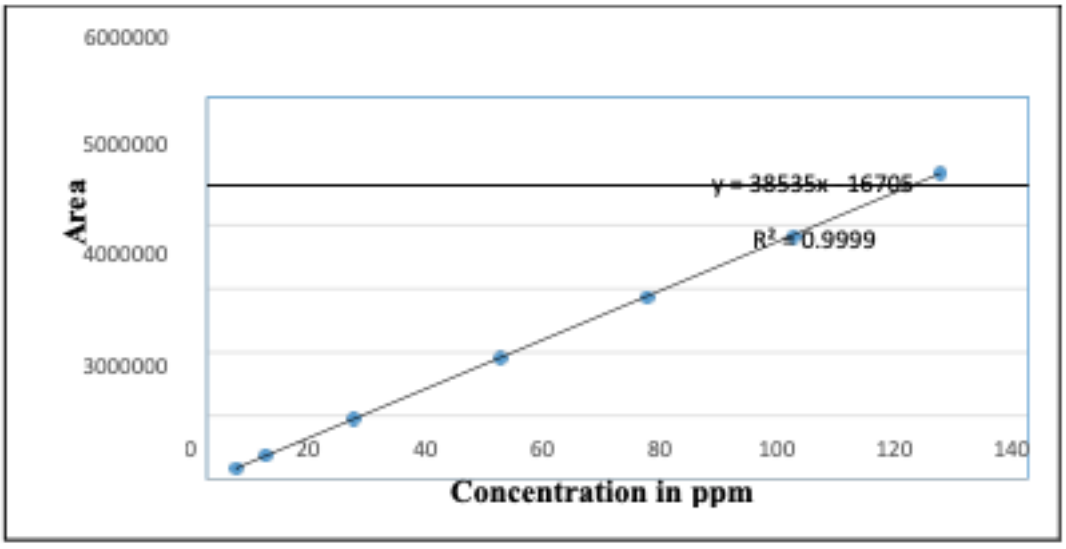


Figure 5.1 Calibration Curve of Venlafaxine HCl

3.3 Compatibility Study

Compatibility study of Venlafaxine HCl was done at specific condition and duration with excipients which are used in the formulation of extended release of pellets. The compatibility study results were determined only based on the physical appearance of API and excipients after specific time duration.

Table 5.3 Compatibility study

TEST PARAMETER	DURATION		
	7 Days	15 Days	30 Days
Physical Appearance	No change	No change	No change

3.4 Particle Size Distribution

The particle size of Venlafaxine HCl loaded sugar spheres was examined across seven different trials. The analysis covered a range of mesh sizes from #16 to #25. It was observed that the mean diameter of the pellets increased as the concentration of ethyl cellulose in the extended-release coating solution was raised.

Table 5. 4 Particle size Distribution

Sieve No. (#)	Cumulative Retain pellets (in %)						
	T 1	T 2	T 3	T 4	T 5	T 6	T 7
16	3.6±0.2	2.3±0.3	2.8±0.3	3.8±0.3	1.4±0.2	2.6±0.2	2.8±0.2
18	93.0±0.3	91.1±0.3	92.1±0.4	89.1±0.04	89.2±0.6	89.8±0.5	90.0±0.6
20	99.3±0.4	99.4±0.4	99.3±0.4	99.3±0.4	99.4±0.3	99.4±0.4	99.3±0.3
25	99.9±0.1	99.9±0.2	99.9±0.2	99.9±0.03	99.9±0.04	99.9±0.04	99.9±0.04

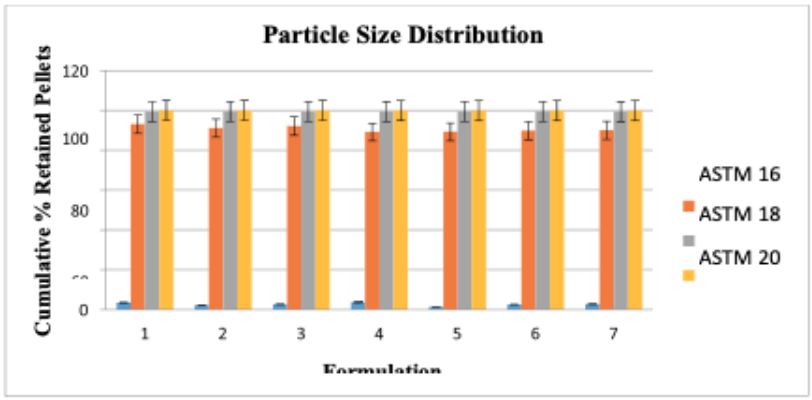


Figure 5.2 Particle Size Distributions

3.5 Flow Properties:

The formulation of generic product of Venlafaxine HCl ER pellets by using various types of polymer like ethyl cellulose 20 cps & 10 cps and medium chain triglycerides to obtained various formulations which properties similar to RLD. There are seven formulation manufactured but only two formulation are optimized on the basis of evaluation parameter of formulation like % Yield, Density, Loss of drying, water content and assay which are these properties similar to EFFEXOR XR.

Table 5.5 Evaluation parameter of formulation

TEST PARAMETER	RESULTS						
	T 1	T 2	T 3	T 4	T 5	T 6	T 7
% yield	98.4	98.9	99.4	98.3	99.6	99.1	99.7
Bulk Density (mg/ml)	0.85±0.03	0.85±0.01	0.83±0.02	0.82±0.02	0.81±0.02	0.80±0.402	0.81±0.02
Loss of drying	0.43±0.10	0.54±0.11	0.72±0.17	0.78±0.2	0.86±0.12	0.61±0.13	0.61±0.2
Water content	3.58±0.01	3.76±0.03	3.67±0.02	3.45±0.17	3.59±0.10	3.62±0.09	3.55±0.19
Assay	99.4	99.7	99.9	99.5	99.8	99.9	99.9

3.6 Dissolution Studies

In-vitro drug release from pellets decreased with increasing amount of polymer because of increase thickness of polymer, which retarded release of drug from pellets. Formulation (T6 & T7) containing polymer ethyl cellulose 20 cps concentration 4% and medium chain triglycerides 0.4% gave drug release 88-92% up to 20 hrs. Similarity factor (F2) value of optimized formulation (T6 & T7) found under the range of 50- 100 and difference factor (F1) value was comes under the range of 0- 50.

Table 5.6 Cumulative % Drug Release in Water Media

TIME	SPECIFICATION (USP)	CUMULATIVE % DRUG RELEASE			
		FORMULATION			
		T 1	T 2	T 3	T 4
2	10 - 30 %	5.23±0.39	7.25±0.55	7.26±0.37	12.16±0.79
4	33 - 53 %	20.45±0.24	25.13±0.75	28.21±0.33	35.36±0.50
8	58 - 78 %	38.08±0.67	44.25±0.80	46.08±0.60	54.95±0.65
12	68 - 88 %	55.01±0.78	62.50±0.42	65.10±0.70	72.90±0.68
20	NLT 80 %	69.93±0.67	77.03±0.65	78.75±0.74	83.03±0.76
Difference factor (f1)		37.87	28.829	25.786	14.921
Similarity factor (f2)		30.808	36.601	39.01	50.135

TIME	SPECIFICATION (USP)	CUMULATIVE % DRUG RELEASE			
		FORMULATION			INNOVATOR (EFFEX0R XR)
		T 5	T 6	T 7	
2	10 - 30 %	27.08±0.73	21.05±1.12	18.06±0.64	15.33±0.31
4	33 - 53 %	57.91±0.61	44.88±0.84	48.10±0.68	43.31±0.30
8	58 - 78 %	79.98±0.71	69.11±0.84	65.95±1.20	70.45±0.30
12	68 - 88 %	89.78±0.59	83.15±0.44	80.93±0.99	82.73±0.14
20	NLT 80 %	97.91±0.75	91.45±0.61	88.25±0.99	91.90±0.28
Difference factor (f1)		16.113	3.127	5.752	
Similarity factor (f2)		49.308	76.8	71.009	

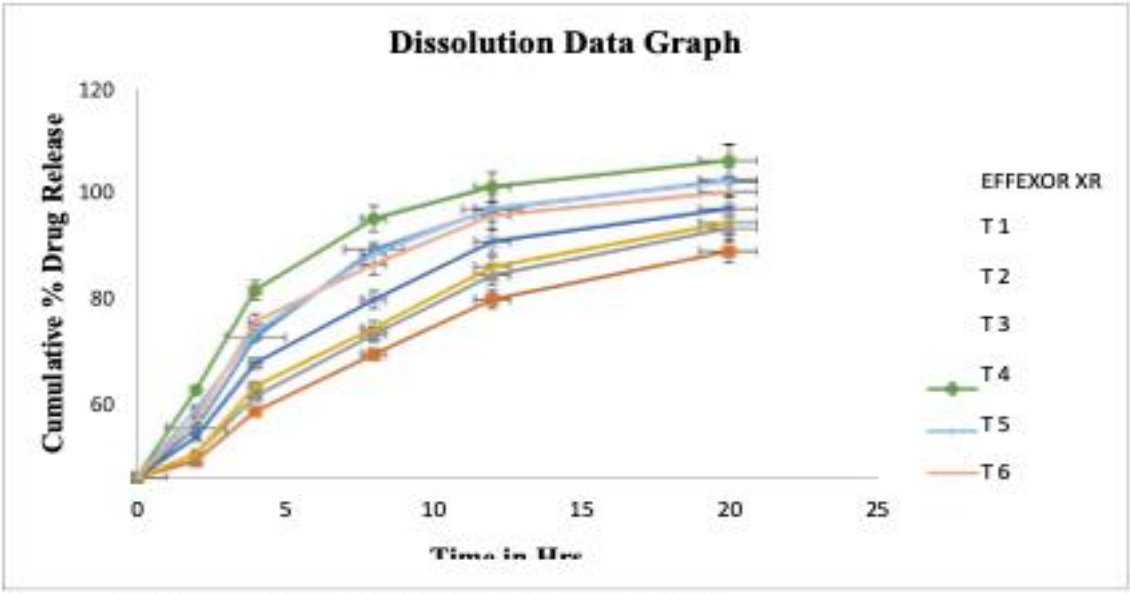


Figure 5.3 Dissolution Graph of trails and RLD

3.7 Drug Release Kinetics

The drug release kinetics profile to obtained from dissolution data which are plotted in different models such as First order, Zero order, Higuchi Matrix Model, Korsmeyer - Peppas Model and the optimized formulation (Trail 6 & 7) which the drug release kinetics profile are similar to EFFEXOR XR. The optimized formulation as well as innovator was followed the first order release kinetic and Higuchi matrix model. The ‘n’ value was found to be indicated that the formulations as well as innovator followed the super case II transport mechanism.

Table 5.7 First order release kinetics data

Time (in Hrs)	Log Cumulative % Drug Remained		
	EFFEXOR XR	Trail 6	Trail 7
0	2	2	2
2	1.9277	1.8973	1.9134
4	1.7535	1.7413	1.7151
8	1.4705	1.4898	1.5321
12	1.2372	1.2266	1.2803
20	0.9084	0.9319	1.07
R^2	0.9834	0.9826	0.9633

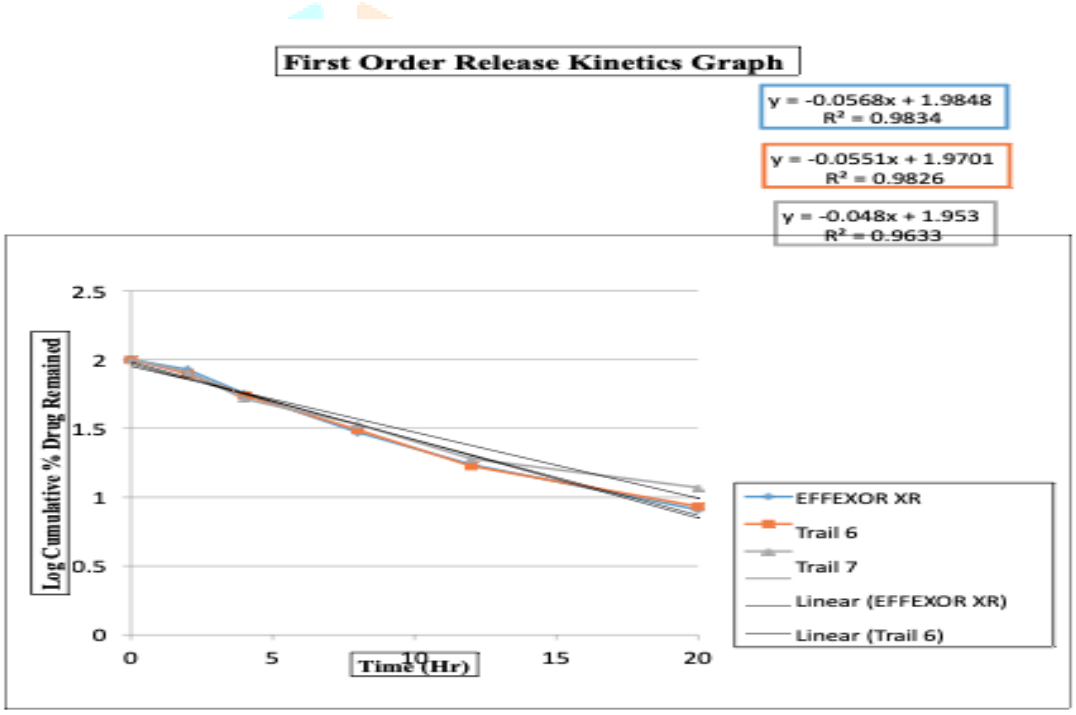


Figure 5.4 First Order Release Kinetics Graph

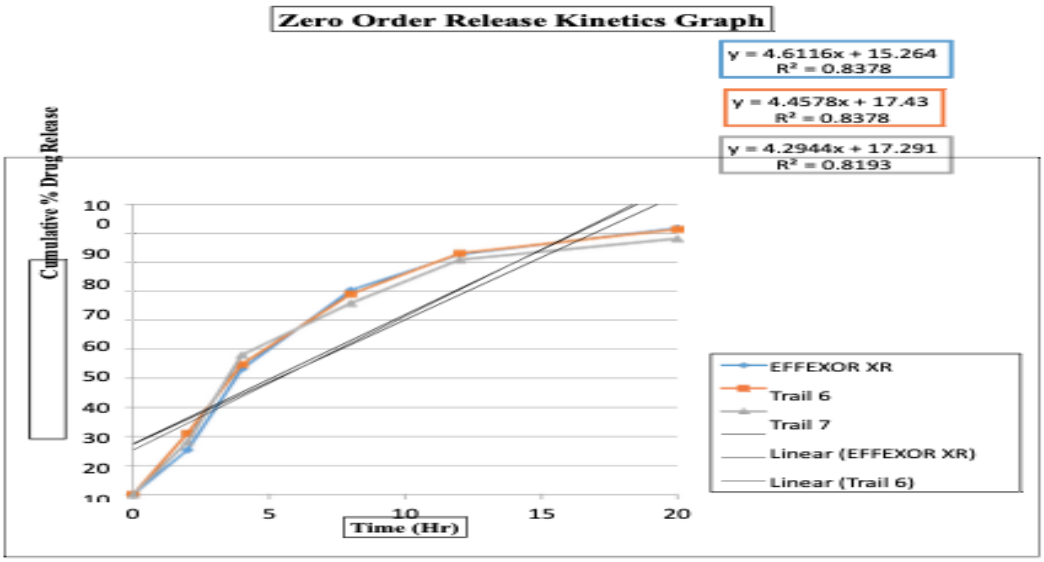


Figure 5.5 Zero Order Release Kinetics of Graph

Table 5.9 Higuchi Matrix Model Data

SQRT Time	Cumulative % Drug Release		
	EFFEXOR XR	Trail 6	Trail 7
0	0	0	0
1.414	15.33	21.05	18.06
2	43.31	44.88	48.1
2.828	70.45	69.11	65.95
3.464	82.73	83.15	80.93
4.472	91.9	91.45	88.25
R^2	0.9459	0.9629	0.9506

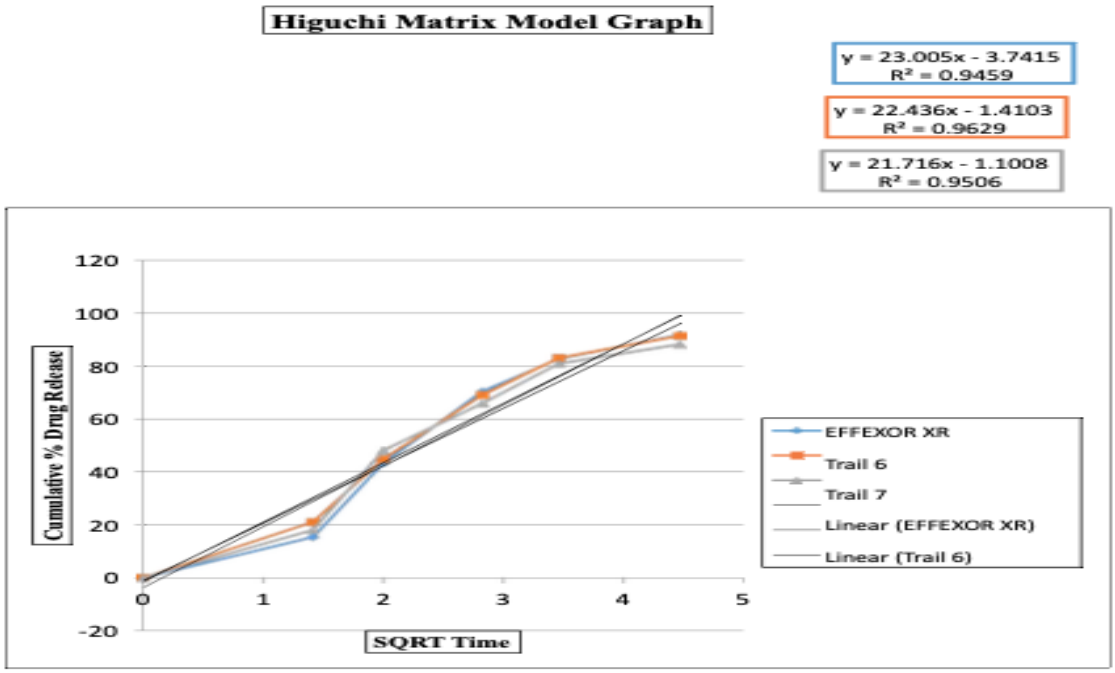


Figure 5.6 Higuchi Matrix Model Graph

Table 5.10 Korsmeyer - Peppas Model Data

Log time	Log Cumulative % Drug Release		
	EFFEXOR XR	Trail 6	Trail 7
0	0	0	0
0.30 1	1.1855	1.3232	1.256 7

0.602	1.6365	1.6520 5	1.682 1
0.903	1.8478	1.8395	1.819 2
1.079	1.9176	1.9198	1.908 1
1.301	1.9633	1.9611	1.945 7
R^2	0.8124	0.7704	0.778 1

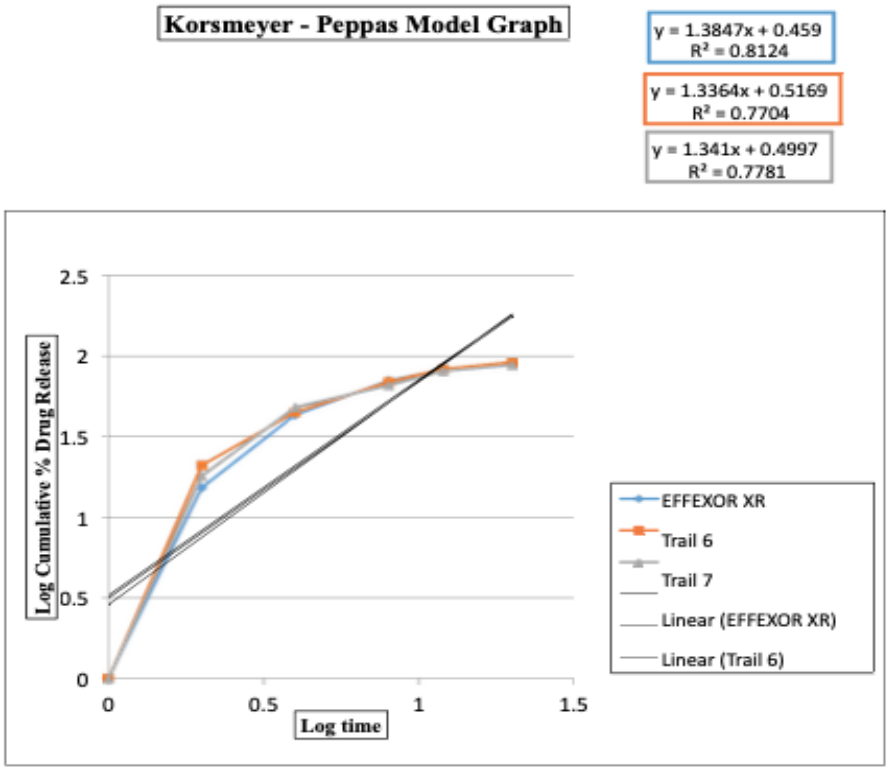


Figure 5.7 Korsmeyer - Peppas Model Graph

3S.8 STABILITY STUDY

Stability study of optimized formulation (Trail 6 & 7) as per ICH guidelines at various condition such as Accelerated (40±2°C/75±5%RH), Intermediate (30 ± 2 °C/65± 5% RH) and Long term (25±2°C/60±5%RH) for 3, 3, 6 months respectively. After completed the duration of the stability condition sample was withdrawn for analysis basis of Physical appearance, Assay, Water content and Loss of drying.

Table 5.11 Stability Study data

Test Parameter	Result					
	Accelerated		Intermediate		Long term	
	Trail 6	Trail 7	Trail 6	Trail 7	Trail 6	Trail 7
Physical appearance	No change	No change	No change	No change	-	-
Assay	99.74	99.63	99.32	99.21	-	-
Water content	3.67	3.72	3.47	3.51	-	-
Loss of drying	0.63	0.65	0.51	0.53	-	-

SUMMARY AND CONCLUSIONS

The objective of this study was to develop and assess the stability of extended-release pellets containing Venlafaxine hydrochloride, aiming for pharmaceutical equivalence with the innovator product Effexor XR® (f2 > 50). The formulation process utilized fluidized bed coating (FBC) with the Wurster technique. The focus was on prolonging the release of Venlafaxine hydrochloride using polymers such as Ethyl cellulose and medium-chain triglycerides. The study encompassed preformulation studies, formulation and evaluation, release kinetics, and stability assessments of the pellets.

Preformulation studies ensured the compatibility of the drug and excipients, revealing satisfactory compatibility based on physical appearance. Flow property evaluations indicated that the optimized formulation exhibited favorable flow properties. The drug content (Assay) of the optimized formulation demonstrated good and reproducible results.

Through in vitro release studies, formulations T 6 and T 7 were identified as optimized, achieving drug release for up to 20 hours with 88-92% release. Various kinetic models were applied to T 6 & T 7, indicating first-order release kinetics, Higuchi matrix model, and super case II transport mechanism. The optimized formulations T 6 & T 7 were deemed pharmaceutical equivalents to the innovator, showing similarity (f2 = 69-77%) in drug release profiles.

Stability studies were conducted on the optimized formulations T 6 & T 7 at accelerated and long-term conditions, and results indicated no significant differences in physicochemical parameters, including assay and physical appearance. The study concluded that extending the drug release was inversely proportional to the coating thickness.

REFERENCES

- Boogaerts T, Degreef M, Covaci A, van Nuijs AL. Development and validation of an analytical procedure to detect spatio-temporal differences in antidepressant use through a
- wastewater-based approach. Talanta. 2019 Mar 15.
- Gong W, Zhu S, Chen C, Yin Q, Li X, Du G, Zhou Y, Qin X. The Anti-depression Effect of Angelicae Sinensis Radix Is Related to the Pharmacological Activity of Modulating the
- Hematological Anomalies. Frontiers in pharmacology. 2019;10.
- Hamed E, inventor; Cima Labs Inc, assignee. Alcohol-resistant extended release dosage forms comprising venlafaxine. United States patent application US 13/715,698. 2013 Jul
- ICH Harmonised Tripartite Guideline, Stability Testing of New drug substances and
- products Q1A (R2) 4th Version dated February 2003.
- Katakam P, Reddy MB, Hwisa NT, Assaleh FH, Dey B, Murthy SV, Chandu BR, Adiki SK. Formulation and evaluation of sustained release venlafaxine tablets using hydrophilic-hydrophobic polymer combinations by melt granulation. Journal of Scientific and Innovative Research. 2014;3(1):49-59.
- Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. Analysis of the second generation antidepressant venlafaxine and its main active metabolite O- desmethylvenlafaxine in human plasma by HPLC with spectrofluorimetric detection. Journal of Chromatography B. 2007 Sep 1;856(1-2):88-94.
- Raveendra Pai. Extended release matrix pellets: preparation and compression into disintegrating tablet, IJDD. 2011:329-339.
- Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. Analysis of the second generation antidepressant venlafaxine and its main active metabolite O- desmethylvenlafaxine in human plasma by HPLC with spectrofluorimetric detection.
- Journal of Chromatography B. 2007 Sep 1;856(1-2):88-94. Raveendra Pai. Extended release matrix pellets: preparation and compression into disintegrating tablet, IJDD. 2011:329-339.

- Reddi SS, Singhvi G, Khosa A, Krishna KV, Saha RN. Determination of Venlafaxine in Bulk and Pharmaceutical Formulations Using Stability Indicating RP-HPLC Method with UV Detector. Current Pharmaceutical Analysis. 2019 Jun 1;15(3):258-65.
- Gaber DM, Nafee N, Abdallah OY. Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs. International journal of pharmaceutics. 2015 Jul 5;488(1-2):86-94.
- Mandrioli R, Mercolini L, Cesta R, Fanali S, Amore M, Raggi MA. Analysis of the second generation antidepressant venlafaxine and its main active metabolite O- desmethylvenlafaxine in human plasma by HPLC with spectrofluorimetric detection. Journal of Chromatography B. 2007 Sep 1;856(1-2):88-94.
- Raveendra Pai. Extended release matrix pellets: preparation and compression into disintegrating tablet, IJDD. 2011:329-339.
- Raveendra Pai. Extended release matrix pellets: preparation and compression into disintegrating tablet, IJDD. 2011:329-339eetharaman S, Nallaperumal N.
- Once Daily Venlafaxine Hydrochloride Extended Release Tablets: Comparison Between Matrix Tablet and Pellets. Int. J. Pharm. Sci. Rev. Res. 2012;13:149-53.
- Yadav K, Yadav D, Srivastava AK. Evaluation of hydrophilic, hydrophobic and waxy matrix excipients for sustained release tablets of Venlafaxine hydrochloride. Drug development and industrial pharmacy. 2013 Aug 1;39(8):1197-206.