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Formulation optimization and characterization of venlafaxine HCL sustained release pellets

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Abstract
Venlafaxine HCl, a serotonin-norepinephrine reuptake inhibitor (SNRI), requires frequent dosing due to its short half-life, which can lead to poor patient compliance and fluctuating plasma levels. This study focuses on the formulation and optimization of sustained release (SR) pellets of Venlafaxine HCl using extrusion-spherization and coating techniques to achieve prolonged drug release. A design of experiments (DoE) approach was employed to optimize critical formulation variables such as polymer concentration, spherization speed, and coating thickness. The optimized formulation showed excellent pellet morphology, desirable drug content, and sustained *in vitro* drug release over a 12–24-hour period. Characterization was carried out using Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and *in vitro* dissolution studies to ensure stability, compatibility, and performance. The developed SR pellets of Venlafaxine HCl can potentially enhance patient adherence and provide more consistent therapeutic outcomes in the management of depression.

Keywords: Sustained release, bioavailability, oral dosage form, buccal, mucosa, pellets

Introduction

The treatment of acute diseases or chronic illness has been achieved by delivery of drugs to the patients for many years. A number of oral dosage forms are available. Some are liquids (e.g., syrups, elixirs, tinctures, suspensions, and emulsions), whereas the most common ones are solids (e.g., tablets & capsules). Tablets and capsules are generally formulated to release the drug immediately after oral administration to hasten systemic absorption. These are called immediate release products. Other products like modified release dosage forms have been developed to release the drug at a controlled rate. The purpose is generally either to avoid contact with gastric fluids (acidic environment) or to prolong drug input in systemic circulation. These drug delivery systems include tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic window. Some drugs also possess solubility problems. Conventional forms often cause problems to the patient, because they maintain therapeutic drug level for only brief duration. This gives rise to sharp fluctuations of drug levels in plasma and in tissue. In such cases, a method of continuous administration of therapeutic agent is desirable to maintain fixed plasma levels.

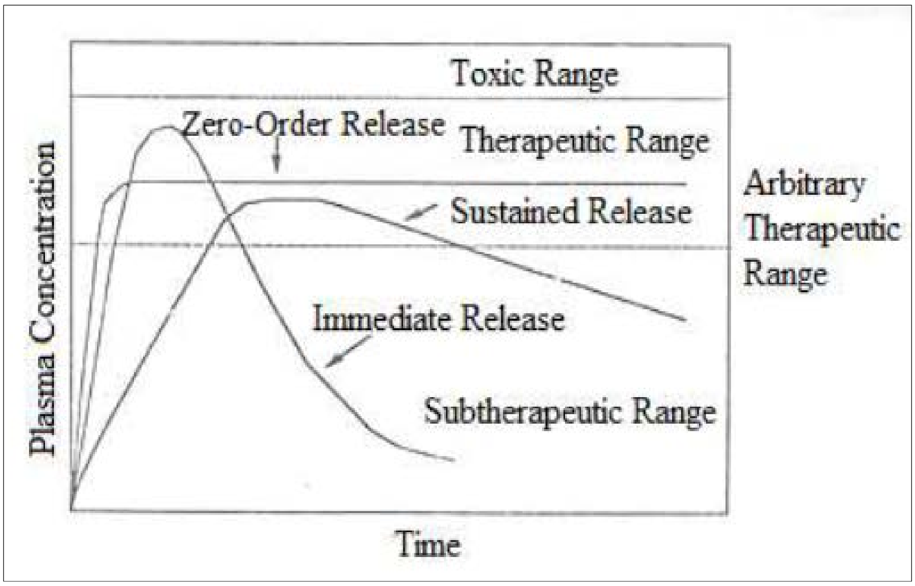

Fig 1: Plasma concentration-time profile

Plasma concentration-time profile

To overcome these problems, Sustained release drug delivery systems were introduced into the market. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of Sustained release drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half-life (t1/2) and duration of pharmacological effect. The time of dosing may also be affected by therapeutic index (TI) of a drug.

Design of sustained release products

Dissolution and diffusion-controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery. Most of these systems are solids, although a few liquids and suspension have been recently introduced. The classifications of such systems are as follows

1. Diffusion controlled systems.
2. Dissolution controlled systems.
3. Dissolution and Diffusion controlled systems.
4. Osmotically controlled systems.
5. Ion exchange systems.

Diffusion Controlled Systems[6]

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. In general two types of sub classes of diffusion systems are recognized they are

A. Réservoir devises.
B. Matrix devises.

A. **Reservoir Devices:** Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane. The nature of the membrane determines the rate of release of drug from the system. The process of diffusion is generally described by Ficks equations,

J = D dc/dx

Where,
J -- Flux (amount/area –time)
D -- Diffusion co-efficient of drug in the membrane (area/time)
dc/dx --rate of exchange in concentration C, with respect to a distance X in the membrane.

Advantages

- Zero order delivery is possible.
- Release rate variable with polymer type.

Disadvantages

- Potential toxicity if system fails.
- System must be physically removed from implant sites.
- Difficult to deliver high molecular weight compounds.
- Generally increased cost per dosage units.

B. Matrix Devices

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi.

$Dm/dh = Cod_h - Cs/2$

Where,
dm = Change in the amount of drug released per unit area.
d_h = Change in the thickness of the zone of matrix that have been depleted of drug.
Co = Total amount of drug in unit volume of matrix.
Cs = Saturated concentration of drug within the matrix.

Advantages

- Can deliver high molecular weight compounds.

- Easier to produce than reservoir devices.

Disadvantages

- Removal of remaining matrix is necessary for implanted systems.
- Cannot obtain zero order release.

Table 1: Details of the material used with manufacturer

S. No.	Materials	Grade	Manufacturer
1	Venlafaxine Hcl	IP	Indian drugs HYD
2	Ethyl cellulose	LR	Indian drugs HYD
3	Povidone (PVPK- 30)	LR	Ontop pharmaceutical Bangalore
4	Diethyl phthalate	LR	Indian drugs HYD
5	Sucrose	LR	Indian drugs HYD
6	Di-potassium hydrogen ortho phosphate	LR	SD Fine chem..Ltd. Mumbai
7	Isopropyl alcohol	LR	SD Fine chem..Ltd. Mumbai
8	Tri ethyl citrate	LR	SD Fine chem..Ltd. Mumbai
9	HPMC 6 cps	LR	Drugs India, Hyderabad
10	HPMC 3 cps	LR	Drugs India, Hyderabad
11	Sugar spears	LR	SD Fine chem..Ltd. Mumbai
12	SLS	LR	Indian drugs HYD
13	SSG	LR	SD Fine chem..Ltd. Mumbai
14	MCCP	LR	SD Fine chem..Ltd. Mumbai

Table 2: Instruments and Apparatus

S.No.	Equipment	Manufacturer
1	Electronic Balance	Tulaman Ltd Hyderabad
2	Mesh # 12, 14, 16, 18,22, 40,60,100	Retsec
3	FTIR spectrophotometer	Thermo Nicolet,USA
4	Analytical Sieve Shaker	Retsec
5	Blender	Rimek
6	Mechanical stirrer	Remi motors, Bombay
7	Fluidized bed coater	Pam Gatt
8	pH meter	Digisum Electronics
9	Dissolution test apparatus (type II)	Electrolab USP Mumbai
10	Rapid mixer granulator	Sainath
11	UV Spectrophotometer	Labomed, inc, USA.
12	Tray dryer	Sai vanitha heating system, Hyderabad
13	Sonicator	Remi motors, Bombay
14	Stability Chambers	Thermo lab
15	Friability test apparatus,	Singhala scientific industries, Ambala.

Construction of calibration curve

Standard plot of Venlafaxine Hcl with 6.8 pH Phosphate buffer

An accurately weighed 100 mg of Venlafaxine Hcl **was** dissolved in pH 6.8 phosphate buffer and made up to 100 ml in volumetric flask (Stock solution- I 1000 µg/ml). From this 2 ml of solution were pipetted out and made up to 50 ml in a 50 ml volumetric flask (Stock solution- II 40 µg/ml). From this the aliquots were prepared whose concentration ranging from 2 to 20 µg/ml and the absorbance were measured at 225 nm against the reagent blank.

Table 3: Calibration curve data for Venlafaxine Hcl at 225 nm

S. No	Concentration in (µg/ml)	Absorbance at (225 nm)
1	0	0
2	2	0.112
3	4	0.204
4	6	0.306
5	8	0.413
6	10	0.498
7	12	0.598
8	14	0.702
9	16	0.785
10	18	0.872
11	20	0.959

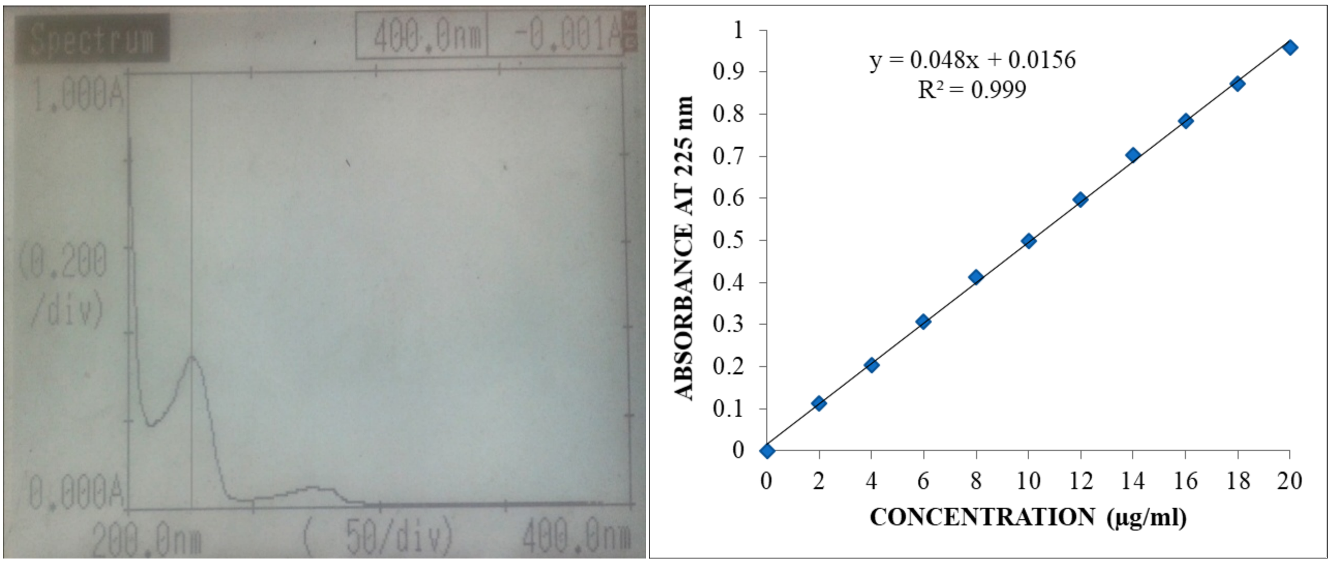

Fig 2: Calibration curve of Venlafaxine HCl

Calibration curve of Venlafaxine HCL

A. Analytical compatibility studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). Infrared (IR) spectra were obtained on a Schimadzu using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm-1 and the resolution was 1 cm^{-1}. FTIR absorption spectra of pure drug and all the polymers used like SUGAR SPEARS, SSG, SLS, MCCP, HPMC-6cps, HPMC-3cps, PVPk-30, EC-10cps and the combination of drug and polymers were shown no significant interaction between drug and polymers.

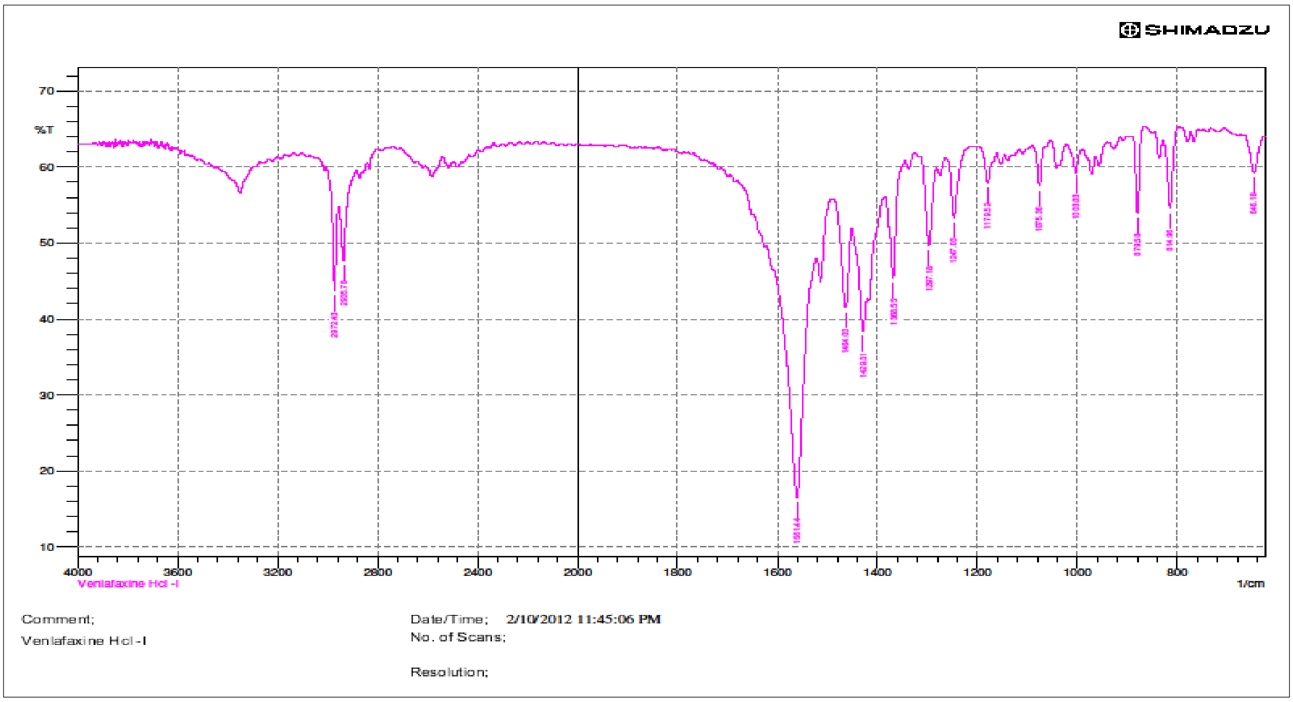

Fig 3: FTIR spectra of venlafaxine HCl

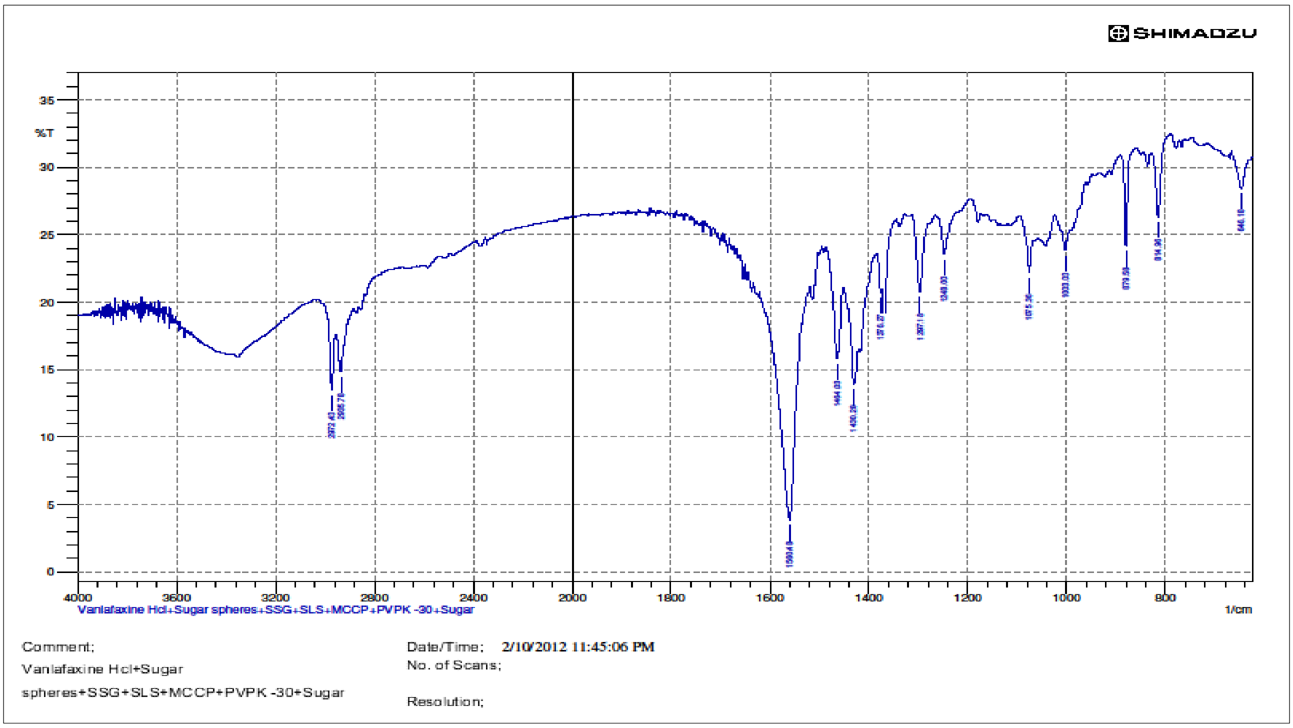

Fig 4: FTIR Spectra of drug coating

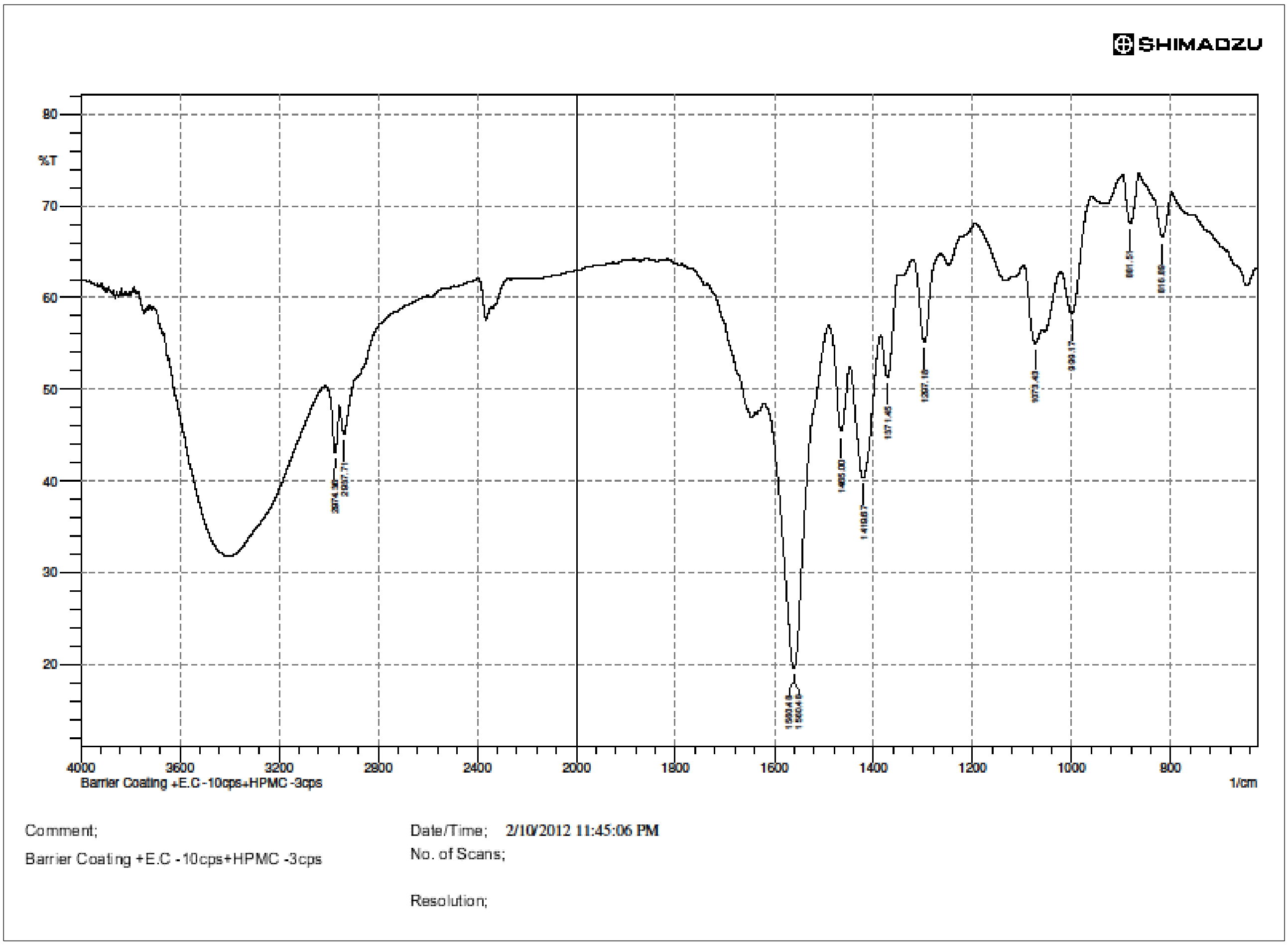

Fig 5: FTIR spectra of barrier coating

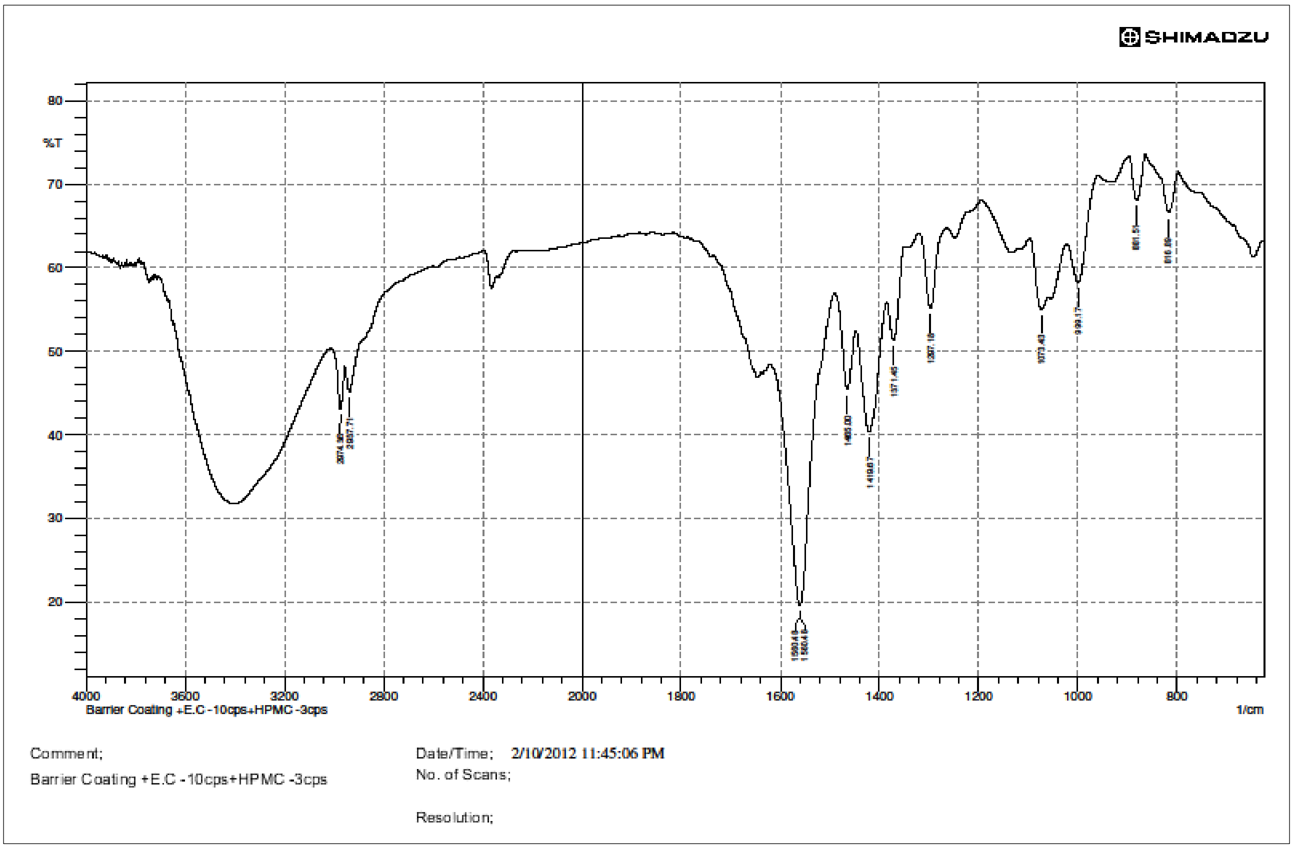

Fig 6: FTIR spectra of sustained release coating

Table 4: Compositions of sustained release Venlafaxine HCL

S. No	Ingredients	Formulation Code (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
	Drug Coating								
1	Venlafaxine Hcl	39.5	39.5	39.5	39.5	39.5	39.5	39.5	39.5
2	Sugar spheres	32.9	32.9	32.9	32.9	32.9	32.9	32.9	32.9
3	Sodium starch glycolate	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
4	SLS	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
5	MCCP	6.7	6.9	7.1	7.3	7.5	7.7	7.9	8.1
6	PVPK-30	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
7	Sugar	5.6	5.5	5.4	5.3	5.2	5.1	5.0	4.9
	Barrier Coating								
8	HPMC 6 cps	4.7	4.7	4.7	4.7	4.7	4.7	4.7	4.7
	Sustained Release Coating								
9	Ethyl cellulose 10 cps	6.7	6.5	6.3	6.1	5.9	5.7	5.5	5.3
10	HPMC 3 cps	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0
11	Tri ethyl citrate	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
12	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
13	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	Glidant								
14	Talc	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	TOTAL WEIGHT (mg)	100	100	100	100	100	100	100	100

Total weight of each capsule is = 100

Evaluation of sustained release pellets

Bulk density and Tapped Density

The loose bulk density (LBD) and tapped bulk density (TBD) of drug pellets were determined. The drug pellets 30 grams were poured into calibrated measuring cylinder (100 ml) then noted initial volume. Tap the measuring cylinder 500 to 1000 times and record the volume was noted. LBD and TBD were calculated using following equation,

LBD = weight of the pellets / volume of the packing

TBD = weight of the pellets / tapped volume of the packing

Angle of repose

Angle of repose of different formulations was measured according to fixed funnel method. Completely dried drug pellets were weighed and passed through the funnel, which was kept at a height ‘h’ from horizontal surface. The passed drug pellets formed a pile of the height ‘h’ above the horizontal surface and the diameter of the pile was measured and the angle of repose was determined for all the formulation using the formula,

$\tan \theta = h / r$

Angle of repose (θ) = $\tan^{-1}$ (h / r)
Where, h is the height of pile and r is the radius.

Compressibility Index
The compressibility index (Carr's Index) of the drug pellets were determined by using the below mentioned equation,

Carr's Index (%) = [(TBD- LBD) × 100] / TBD

Hausner's Ratio
Hausner's ratio is an indirect index of ease of drug pellets flow. It is calculated by the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25)

Table 5: Limits for characterization of Drug pellets[61].

S.no	Type of flow	Angle of repose	Carr's index	Hausner's ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40(aid not needed)	16-20	1.19-1.25
4	Passable	41-45(may hang up)	21-25	1.26-1.34
5	Poor	46-55(must agitate)	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.54
7	Very very poor	>66	>38	>1.60

Table 6: Results for Derived and Flow properties

Formulation Code	Bulk density ± SD	Tapped density ± SD	Angle of Repose ± SD	Carr's Index ± SD	Hausner's ratio ± SD
F1	0.74±0.011	0.86±0.015	31.15±0.23	13.9±0.02	1.16±0.09
F2	0.73±0.021	0.85±0.013	33.04±0.15	14.1±0.06	1.16±0.08
F3	0.73±0.016	0.84±0.08	33.72±0.09	13.1±0.09	1.15±0.07
F4	0.76±0.025	0.86±0.0112	32.98±0.06	11.6±0.013	1.13±0.08
F5	0.73±0.017	0.84±0.021	32.45±0.05	13.1±0.012	1.15±0.014
F6	0.74±0.042	0.85±0.022	31.69±0.02	12.9±0.09	1.14±0.05
F7	0.75±0.06	0.86±0.051	34.15±0.21	12.7±0.07	1.14±0.08
F8	0.73±0.07	0.85±0.012	30.73±0.08	14.1±0.06	1.16±.0.02

Moisture Content (by Karl-Fisher)

$$\text{Moisture Content} = \frac{V \times F \times 100}{\text{Weight of sample (mg)}}$$

Friability
The Roche friability test apparatus was used to determine the friability of the pellets. Twenty gram's pre-weighed pellets were placed in the apparatus and operated for 100 revolutions and then the pellets were reweighed. The percentage friability was calculated according to the following formula.

$$\%\,\text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X100$$

Determination of drug content (Assay)
An accurately weighed quantity of the sustained release pellets equivalent to 35mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the pellets and extracting with aliquots of 6.8 buffer repeatedly. The extract was transferred to a 100ml volumetric flask and the volume was made up using 6.8buffer. The solution was filtered and the area under the curve was measured by using U V analysis method.

Table 7: Results for Drug content, Friability, Moisture Content, Particle size.

Formulation code	Drug content In mg	Friability	Moisture Content	Particle size
F1	33.79	0.71	3.02	692.01 ± 0.57
F2	33.91	0.69	2.96	689.20 ± 0.32
F3	34.17	0.63	2.8	679.13 ± 0.48
F4	34.48	0.46	1.8	676.29± 0.25
F5	33.81	0.68	2.53	683.39± 0.368
F6	33.98	0.73	2.39	687.51± 0.98
F7	34.25	0.62	1.97	691.58 ± 0.62
F8	34.43	0.57	2.31	700.54± 0.63

Determination of mean particle size of pellets
Particle size determination of pellets was carried out by sieve analysis method. A mixture quantity of dried pellets was placed on the top side of the sieve. Then witch on the instrument for specified time with specified rpm. After the completion of sieving separate the individual sieve and weigh the pellets Then calculate the average size of the pellets range is 676.29 - 700.54 µm.

Table 8: Particle size analysis by sieve analysis method for F1

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	14.4	24480	∑nd / ∑n 692.01 ± 0.57
2	22	710	812.2	576875	
3	44	325	12.5	4062.5	
4	60	250	24.7	6175	
5	85	180	17.9	3222	
6	100	150	8.6	1290	
7	120	125	-	-	
			∑n= 890.3	∑nd=616104.5	

Table 9: Particle size analysis by sieve analysis method for F2

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	12.3	20910	∑nd / ∑n 689.20 ± 0.32
2	22	710	844.5	599595	
3	44	325	13.2	4290	
4	60	250	32.5	8125	
5	85	180	15.4	2772	
6	100	150	5.7	855	
7	120	125	-	-	
			∑n= 923.6	∑nd=636547	

Table 10: Particle size analysis by sieve analysis method for F3

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	11.2	19040	∑nd / ∑n 679.13 ± 0.48
2	22	710	832.6	591146	
3	44	325	17.4	5655	
4	60	250	44.6	11150	
5	85	180	20.1	3618	
6	100	150	3.4	510	
7	120	125	-	-	
			∑n= 929.3	∑nd=631119	

Table 11: Particle size analysis by sieve analysis method for F4

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	25.6	43520	∑nd / ∑n 700.54± 0.63
2	22	710	812.3	576733	
3	44	325	17.1	5557.5	
4	60	250	24.7	6175	
5	85	180	12.3	2214	
6	100	150	4.2	630	
7	120	125	-	-	
			∑n= 906.2	∑nd=634829.9	

Table 12: Particle size analysis by sieve analysis method for F5

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	14.5	24650	∑n / ∑nd 683.39± 0.368
2	22	710	849.3	603003	
3	44	325	15.4	5005	
4	60	250	34.8	8700	
5	85	180	29.1	5238	
6	100	150	3.4	510	
7	120	125	-	-	
			∑n= 946.9	∑nd=647106	

Table 13: Particle size analysis by sieve analysis method for F6

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	11.3	19210	∑nd / ∑n 687.51± 0.98
2	22	710	824.9	585679	
3	44	325	12.5	4062.5	
4	60	250	38.4	9600	
5	85	180	14.3	2574	
6	100	150	2.6	390	
7	120	125	-	-	
			∑n= 904	∑nd=621515.5	

Table 14: Particle size analysis by sieve analysis method for F7

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	12.4	21080	∑nd / ∑n 691.58 ± 0.62
2	22	710	824.6	585466	
3	44	325	13.2	4290	
4	60	250	35.9	8975	
5	85	180	29.3	5274	
6	100	150	2.1	315	
7	120	125	-	-	
			∑n=904.3	∑nd=625400	

Table 15: Particle size analysis by sieve analysis method for F8

S. No	Sieve No	Arithmetic mean size of opening (µm)	Weight retained on a sieve (g)	Arithmetic mean size µm X weight	Average particle size (µm) Mean ± SD*
1	10	1700	9.4	15980	∑nd / ∑n 676.29± 0.25
2	22	710	847.3	601583	
3	44	325	31.5	10237.5	
4	60	250	33.7	8425	
5	85	180	24.1	4338	
6	100	150	1.5	225	
7	120	125	-	-	
			∑n= 947.5	∑nd=640788.5	

In vitro drug release studies

The *In-Vitro* drug release studies were carried out using paddle type dissolution apparatus. Drug loaded pellets were weighed equivalent to 100 mg of drug was introduced into the 900 ml of dissolution medium (1.2 pH HCl buffer) maintained at 37±0.5 ºC with paddle rotating at 100 RPM. Sample was withdrawn for 2 hrs. And then use 6.8 buffer for dissolution medium. The samples were withdrawn in time intervals respectively i.e., 0, 2, 4, 8, 12, 18, 24 hrs. Aliquots were withdrawn and the same volume of fresh medium was refilled for the maintenance of sink condition. The analysis was performed by U V analysis method. The drug release were calculated by using the below mentioned formula.

Table 16: Dissolution studies profile for formulations F1-F4

Time (hr)	SQRT of time	% Cumulative drug release			
		F1	F2	F3	F4
0	0	0	0	0	0
2	1.414	13.6	15.3	16.8	17.6
4	2	25.3	26.8	30.8	35.4
8	2.82	43.8	43.3	46.9	54.7
12	3.46	64.9	66.1	69.7	73.9
18	4.242	78.6	81.7	83.2	88.4
24	4.898	89.4	92.6	94.7	96.7

Table 17: Peppa’s data for F1-F4

Log time	Log of % Cumulative drug release			
	F1	F2	F3	F4
0	0	0	0	0
0.301	1.133	1.184	1.225	1.245
0.602	1.403	1.428	1.488	1.549
0.903	1.641	1.636	1.671	1.737
1.079	1.812	1.82	1.843	1.868
1.255	1.895	1.912	1.92	1.946
1.38	1.951	1.966	1.976	1.985

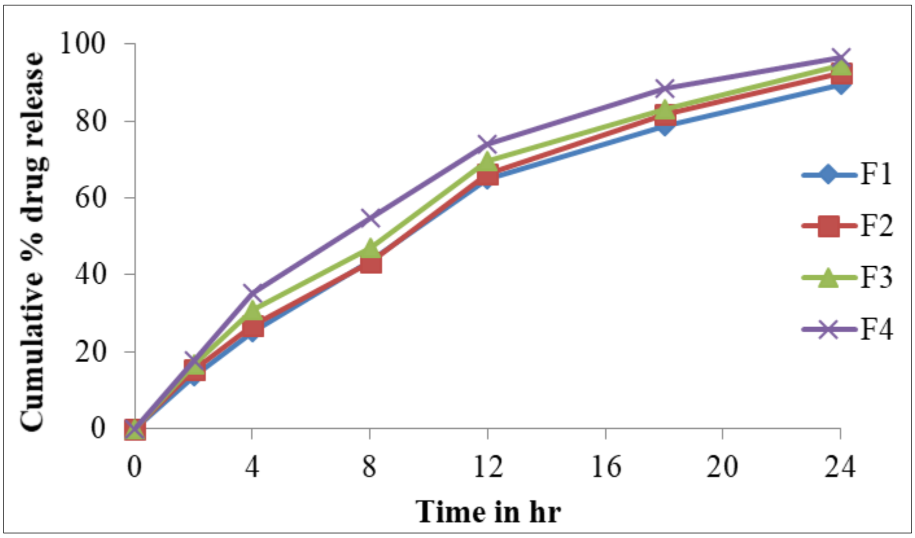

Fig 7: Comparative *In vitro* drug release data for Formulation F1-F4

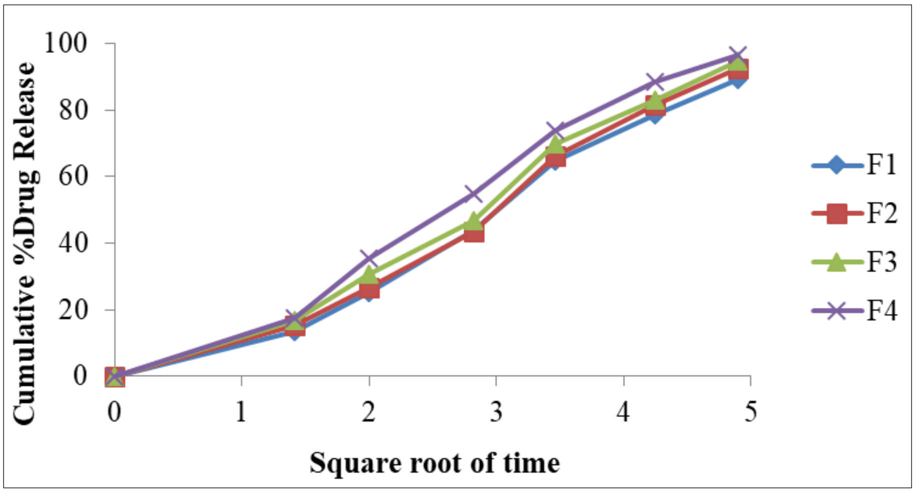

Fig 8: Comparative Higuchi Drug Release Data for Formulation F1-F4

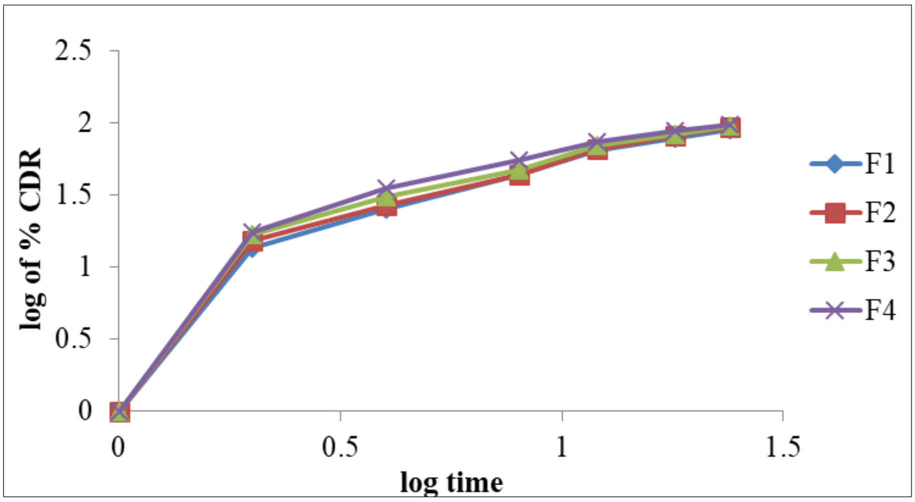

Fig 9: Comparative Peppa's drug release data for formulation F1-F4

Table 18: Dissolution studies profile for formulations F5-F8

Time (hr)	SQRT of time	% Cumulative drug release			
		F5	F6	F7	F8
0	0	0	0	0	0
2	1.414	18.4	19.2	21.6	22.9
4	2	40.6	48.4	59.8	68.1
8	2.82	61.7	72.6	78.9	89.6
12	3.46	78.5	84.7	92.3	99.2
18	4.242	90.6	97.34	98.9	
24	4.898	99.3			

Table 19: Peppa's data for F5-F8

Log time	Log of % Cumulative drug release			
	F5	F6	F7	F8
0	0	0	0	0
0.301	1.264	1.283	1.334	1.359
0.602	1.608	1.684	1.776	1.833
0.903	1.79	1.86	1.897	1.952
1.079	1.894	1.927	1.965	1.996
1.255	1.957	1.988	1.995	
1.38	1.996			

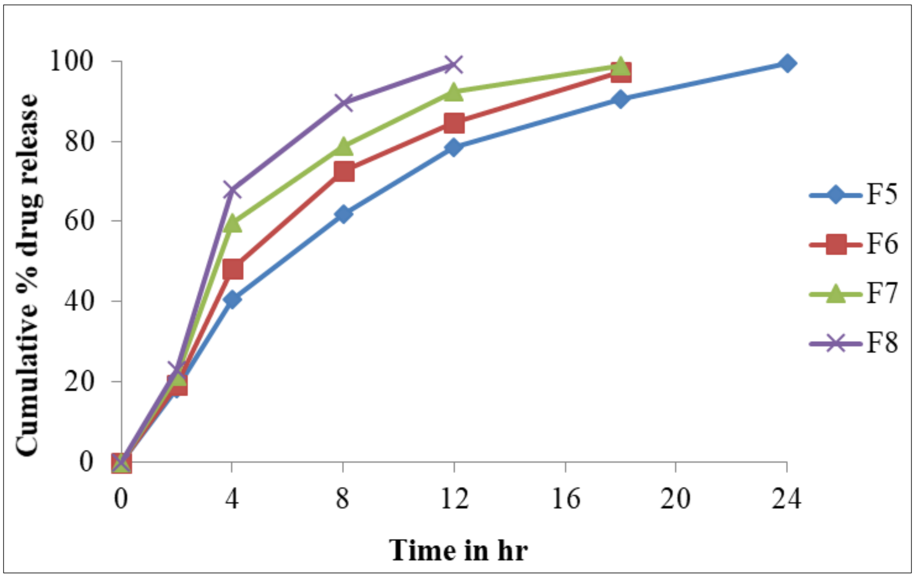

Fig 10: Comparative *In vitro* drug release data for Formulation F5-F8

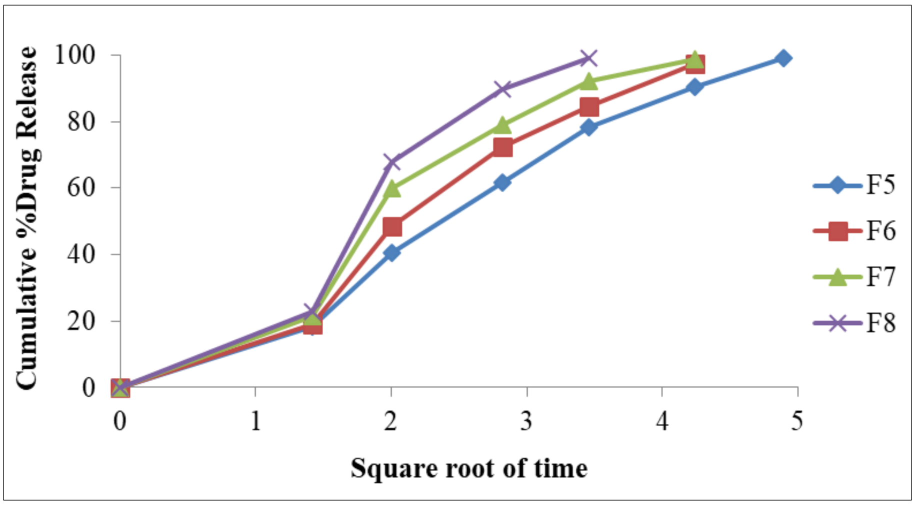

Fig 11: Comparitive Higuchi Drug Release Data for Formulation F5-F8

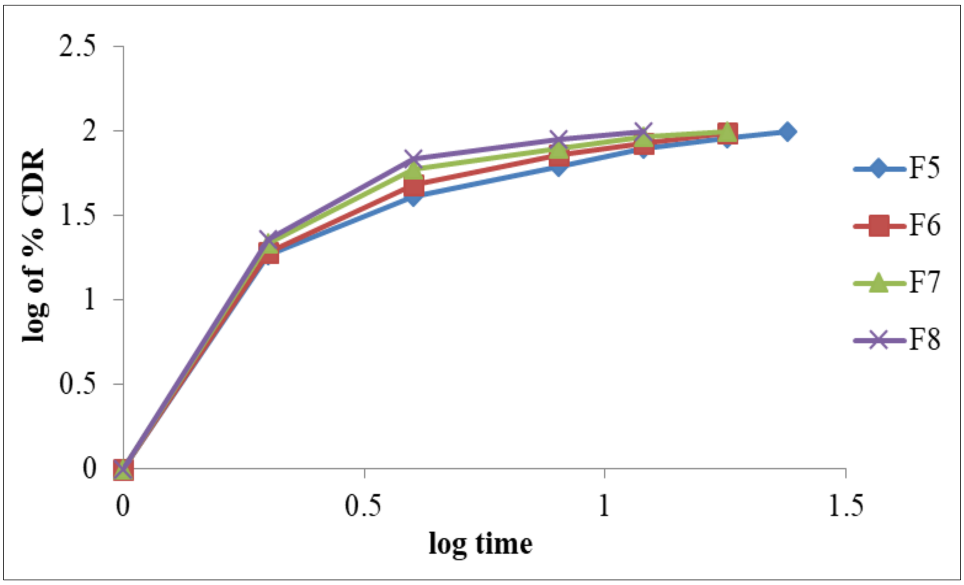

Fig 12: Comparitive Peppa's drug release data for formulation F5-F8

Stability study

The formulation F5 was selected and the stability studies were carried out at accelerated condition of 40±2 °C, 75±5% RH conditions, stored in stability chamber the pellets were packed in transparent polyethylene bags, and kept in above said condition for period of three months. The pellets were analyzed periodically for their physical appearance, moisture content, assay and *in-vitro* drug release.

Table 20: Stability studies of best formulation (F5)

Stage	Assay (%)	Moisture content %	% Cumulative drug release			
			2hr	4hr	8hr	12hr
Specification	33.25 to 36.75	NMT 3.0	NMT 35	30 to 60	50 to 80	60 to 90
Initial	35.70±0.4	1.6	33.5±0.5	48.5±0.3	66.6±0.5	79.1±0.7
40/75 -1M	34.8±0.6	1.7	33.20±0.4	47.5±0.5	65.5±0.3	78.6±0.5
40/75 –2M	34.1±0.6	1.9	33.09±0.4	46.5±0.5	64.7±0.3	76.5±0.5
40/75 –3M	39.6±0.3	1.96	33.03±0.7	46.01±0.6	64.6±0.6	76.3±0.7

Results and Discussion

The present study was undertaken to formulation sustained release pellets. The study involves preformulation studies of drug and excipients, formulation and processing development along with evaluation of pellets made with the optimized formulation. Finally sustained release pellets were evaluated by *In Vitro* method.

Table 22: Characterization of API powder

S. No.	Test	Specification	Result's
1	Description	A white to off-white coloured powder	A white to off-white coloured powder
2	Identification	The obtained sample was examined by Infrared absorption spectral analysis and compared with standard	Complies
2	Solubility	Freely Soluble in water is 527mg/ml,	Freely Soluble in water
3	Moisture Content (by Karl-Fisher)	NMT 0.3%w/w	0% w/w
4	Assay(as Venlafaxine) by U V analysis	Not less than 95.0% and not more than 105% w/w	100% w/w
5	Melting Point	215-217^{0}C	215 ºC
6	Bulk density	0.6 to 0.80 gm/ml	0.65 gm/ml
	True density	0.7 to 0.9 gm/ml	0.72 gm/ml
	Haussner's Ratio	1.35 to 1.45	1.42
	Compressibility Index (%)	21 to 25	23.54
	Angle of repose	46 to 55	52.16

Drug - Excipients compatibility study

A. Physical Observation

Compatibility studies by accelerated stability testing showed that there was no physical change or interaction between drug and selected excipients. Based on the physical compatibility results, the innovator product composition the below excipients were selected for formulation development.

Table 23: Physical Observation

S. No	Polymers	D:P ratio	Physical Observation					
			First Day		After two week's		After four week's	
			25±2⁰C,60±5%	40±2°C,75±5%	25°C±2⁰C,60±5%	40±2°C,75±5%	25°C±2⁰C,60±5%	40±2°C,75±5%
1.	Venlafaxine	1	NC	NC	NC	NC	NC	NC
2.	Sugar Spheres	1:1	NC	NC	NC	NC	NC	NC
3.	SSG	1:1	NC	NC	NC	NC	NC	NC
4.	SLS	1:1	NC	NC	NC	NC	NC	NC
5.	MCCP	1:1	NC	NC	NC	NC	NC	NC
6.	PVPK-30	1:1	NC	NC	NC	NC	NC	NC
7.	Sugar	1:1	NC	NC	NC	NC	NC	NC
8.	Sugar Spheres: SSG: SLS: MCCP: PVPK-30: Sugar	1:1:1:1:1:1:1:1	NC	NC	NC	NC	NC	NC
9.	S.NO 7:HPMC-6cps	1:1:1	NC	NC	NC	NC	NC	NC
10.	S.NO 8:EC-10cps:HPMC-3cps	1:1:1:1	NC	NC	NC	NC	NC	NC

D: P = Drug Polymer Ratio (gram's)
NC: No Change

Table 24: Analytical compatibility studies by FTIR

Venlafaxine HCl	
Frequency cm^{-1}	**Group assigned**
2972.43, 2935.78	C-H Stretching (alkane)
1561.44, 1464.03, 1429.31	C=C Stretching (aromatic)
1368.55	C-O Stretching (phenols)
1297.18,1247.03	C-O Stretching (alcohols)
1179.52, 1075.36, 1003.03	C-N Vibrations
879.58, 814.96, 646.18	C-H bending (aromatic)
Drug Coating	
2972.43, 2935.78	C-H Stretching (alkane)
1464.03, 1430.28	C=C Stretching (aromatic)
1376.27	C-O Stretching (phenols)
1297.18, 1248.00	C-O Stretching (alcohols)
1075.36, 1003.03	C-N Vibrations
879.58, 814.96, 646.18	C-H bending (aromatic)
Barrier Coating	
3628.26, 3565.57	O-H Stretching (free)
3404.51, 3395.83, 3385.22, 3364.96	N-H Stretching
3015.83	C-H Stretching (alkene)
2972.43, 2936.75, 2878.88, 2854.77	C-H Stretching (alkane)
1652.10, 1647.28, 1637.64, 1627.03	C=C Stretching (alkene)
1516.11, 1465.96, 1427.39, 1416.78	C=C Stretching (aromatic)
1369.52, 1298.15, 1248.00, 1076.33, 1002.06	C-N Vibrations
880.54, 814.96,, 646.18	C-H bending (aromatic)
Sustained Release Coating	
2974.36, 2937.71	C-H Stretching (alkane)
1560.48	N-H bending
1465.00, 1419.67	C=C Stretching (aromatic)
1371.45, 1217.18, 1073.43, 999.17	C-N Vibrations
881.51, 816.89	C-H bending (aromatic)

The Drug and polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). The physicochemical compatibility of the drug and the polymer was established through FTIR studies. IR spectral analysis of venlafaxine Hcl showed the peaks at wave numbers of, 2972.43, 2935.78,C-H Stretching (alkane);1561.44, 1464.03, 1429.31,C=C Stretching (aromatic);1368.55,C-O Stretching (phenols); 1297.18,1247.03,C-O Stretching (alcohols);1179.52, 1075.36, 1003.03,C-N Vibrations; 879.58, 814.96, 646.18, C-H bending (aromatic) confirming the purity of drug with standard respectively. In the physical mixture of Venlafaxine Hcl with HPMC, EC, PVP, MCCP, SUGAR, SSG,and SLS, the major peaks obtained were 2974.36, 2937.71, C-H Stretching (alkane); 1560.48, N-H bending, 1465.00, 1419.67, C=C Stretching (aromatic); 1371.45, 1217.18, 1073.43, 999.17, C-N Vibrations; 881.51, 816.89, C-H bending (aromatic). However, the additional peaks were obtained in physical mixtures which could be due to presence of polymers but there is no influence in the drug peaks, which indicates there is no significant interaction between the drug and polymers and the entrapment of drug only by physical process.

Evaluation of sustained release pellets

Micromeritic properties

The formulation of Venlafaxine Hcl pellets were evaluated for derived and flow properties include bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio after carry out the formulations.

Moisture Content (by Karl-Fisher)

The formulation of Venlafaxine Hcl pellets were evaluated for Moisture Content after carry out the formulations.

Determination of drug content (Assay)

The drug content of the all-sustained release pellets formulations was found to be in the range between 33.79to 34.48 mg.

Friability

Friability is the measurement of pellets strength. Electrolab EF-2 friabilator (USP) was used for testing the friability**.** Lower friability values indicate good mechanical strength. pellets of known mass were placed in Friability tester and subjected to impact testing at 25 RPM for 5 min. Pass the pellets through a sieve of mesh size 16 weight of pellets retained on the sieve was noted and the friability was calculated using the following equation.

Friability= (1-initial weight/weight retained after 100 rotation) X100

The sustained release pellets formulations were calculated.

Determination of mean partical size of pellets

The pellets size was determined by sieve analysis method and the average particle size of all batches of pellets were given in Table No: 15 to 22. The particle sizes of the SR pellets were found to be in the range of 676.29 µm – 700.54µm.

***In-vitro* drug release studies**

The *In Vitro* drug release was conducted in pH 6.8 buffer, the samples are withdrawn for 2, 4, 8, 12, 18, and 24.

Formulations F1, F2, F3, F4, F5, F6, F7, and F8 containing Combination of HPMC, EC, PVP, SUGAR and MCCP gave a reasonable Venlafaxine Hcl SR pellets release up to 24 hr.

The formulations F1, F2, F3, F4, F5, F6, F7, and F8 has shown release 89.4%, 92.6%, 94.7%, 96.7% 99.3%97.34% 98.9% and 99.2% respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 0.770341007, 0.703113753, 0.663783, 0.657772, 0.618482503, 0.671564096, 0.641647, and 0.673743 respectively. which confirms that the diffusion mechanism involved in the drug release was Non fickian release in all formulations.

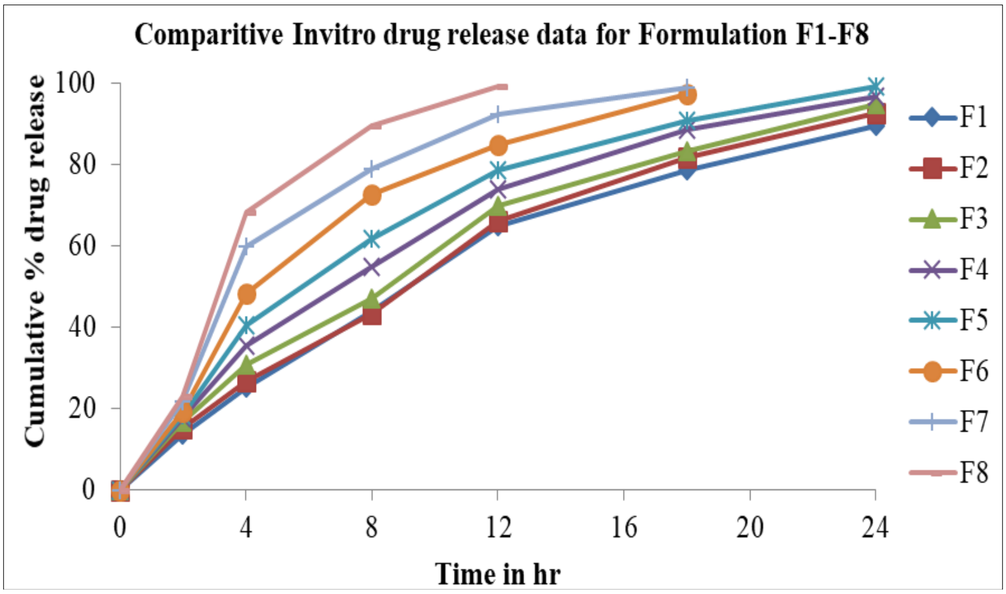

Fig 13: *In-vitro* release data for formulations F1-F8

***In-vitro* Release kinetics**

Data of *in-vitro* release were fit into different equations and kinetic models to explain the release kinetics of Venlafaxine Hcl from the SR pellets. The kinetic models used were a zero-order equation, higuchi's model and peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. i.e. Cumulative percentage release of drug Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppas). To know the mechanism of drug release of Venlafaxine Hcl from the SR pellets, the drug release data was fit into higuchi's models.

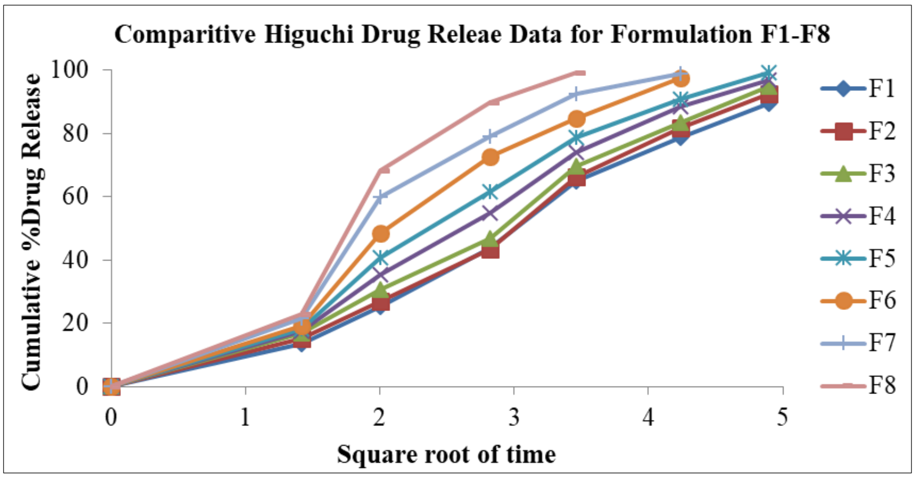

Fig 14: Higuchi data for formulations F1-F8

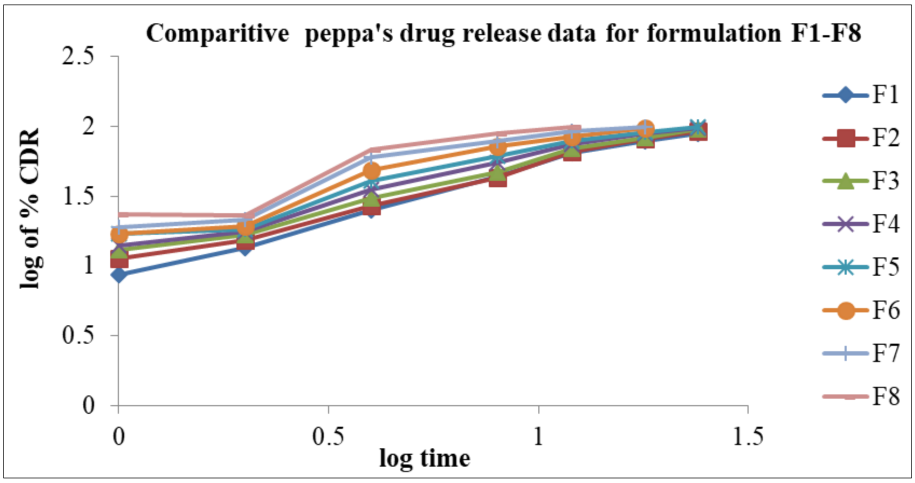

Fig 15: Peppas data for formulation F1-F8

Table 16: Diffusion characteristics of Venlafaxine HCL formulation

Formulation code	Correlation coefficient values (r^2)		Diffusion exponent value (n)
	Zero Order	Higuchi's Model	
F1	0.975879377	0.986361071	0.770341007
F2	0.978585222	0.98677747	0.703113753
F3	0.972254	0.990361	0.663783
F4	0.958877	0.991833	0.657772
F5	0.943399555	0.990046419	0.618482503
F6	0.93993951	0.984015935	0.671564096
F7	0.904802	0.97233	0.641647
F8	0.931401	0.96836	0.673743

Table 17: Diffusion exponent drug release mechanism

S. No.	Diffusion exponent value (n)	Drug release mechanism
1	< 0.45	Fickian release
2	0.45 to 0.89	Non fickian release
3	0.89	Case II transport
4	> 0.89	Super case II transport

Stability study

The stability studies of formulation F5 were carried out at accelerated condition of 40±2 °C, 75±5% RH conditions, periodically checked for appearance, and *in-vitro* drug release.

Conclusion

Venlafaxine Hcl as an antidepressant it was selected for design of sustained release in the form of pellets. venlafaxine Hcl is well known drug widely used for the treatment of antidepressant and they are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake level. However, due to its short half-life (5hr) and low bioavailability (45%), traditional sustained release venlafaxine Hcl solid dosage forms need to be administrated once a day.

The prepared venlafaxine Hcl were characterized for their bulk density, tap density, angle of repose, friability, moisture content, Carr's Index, Hausner's ratio, drug content, mean particle size, and *In Vitro* drug release. The pellets were prepared by layering method and varying the polymeric ratio.

The *In Vitro* drug release revealed that batch F5 was having 99.3 cumulative releases at the end of 24^{th} hour When comparing all the formulations F5 contains HPMC 3cps (1.7 mg), EC (5.9 mg), MCCP (7.5) and sugar (5.2 mg) was the best one in all the aspects. The sustained release venlafaxine

Hcl followed Non fickian release diffusion. Hence, the formulation F5 has met the objectives of the present study. Formulation F5 holds promise for further *In Vivo* studies, which can be extrapolated for the development of sustained release drug delivery system.
Stability studies conducted according to ICH guidelines carried out for a period of 3 months in short term period. The results were within the specification at accelerated conditions concludes our formulation is stable.
As an extension of this work bioavailability, pharmacokinetic and *In Vivo* studies can be done in future to develop as suitable candidate for a novel drug delivery system.

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