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DESIGN, FORMULATION AND CHARACTERIZATION OF VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE MULTIPARTICULATE SYSTEMS

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ABSTRACT

The main objective of present investigation is to formulate and evaluate the extended release pellets of venlafaxine hydrochloride a weakly basic and antidepressant drug belongs to serotonin-norepinephrine reuptake inhibitor class having high permeability and high solubility. Rational use of the selection of dosage form is to minimize variation in residence time, less susceptible to dose dumping, to facilitate accurate delivery of small quantity of potent drug, reduced potential side effects without lowering drug bio-availability. Extended release pellets of venlafaxine hydrochloride were prepared employing different concentrations of eudragit, ethylcellulose, hypromellose and surelease in different combinations as a rate retarding polymer by using drug layering technique. The quantity of polymers to achieve the desired extended drug release about 20 hours and the similarity with the reference product was determined. Totally 8 formulations were prepared and are evaluated for hardness, friability, drug content, *In-vitro* drug release. From the Results it was concluded that all the formulations were found to be within the Pharmacopoeial limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Formulation F8 containing combination of 10% ethyl Cellulose N-50, 13.9% polyethylene gylcol-6000 and 13.6% hypromellose, is the most similar formulation when compared with that of marketed product. The optimized formulation follows first order kinetics and Higuchi's model, and hence, the mechanism of drug release was found to be diffusion controlled.

KEYWORDS: Venlafaxine hydrochloride, Extended Release, pellets, Ethylcellulose, Eudragit.

INTRODUCTION

The oral route of administration is the most convenient and commonly used method of drug delivery system for the systemic delivery of drug through various pharmaceutical products of different dosage forms. Among several approaches, multiparticulate systems have gained much attention in the last two decades, due to their flexibility in formulation development and the therapeutic benefits they provide. Pellets are small, free flowing spherical or semi spherical units containing mixture of drug and excipients ranges from 0.5mm to 1.5mm intended to administer through oral route of administration. Multiple-unit sustained release dosage forms such as pellets have many therapeutic advantages in comparison with the single-unit dosage forms. Pellets distribute homogeneously in the gastrointestinal tract (GI tract) and provide several benefits. They maximize drug absorption and reduce peak plasma fluctuations and minimize the risk of local GI tract irritation and dose dumping. Pellets help in reducing dosing frequency and improving patient compliance and thus in enhancing the drug's safety and efficacy. Pelletization is the most promising technique for the preparation of multi particulate drug delivery systems.[1,2] The design of oral extended release drug delivery systems should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug concentration in the target tissue and optimization of the therapeutic effect of a drug by extending its release in the body with lower and less frequent dose.[3,4]

Objective of present study is aimed to design, formulate and evaluation of venlafaxine hydrochloride ER pellets, to enhance its oral bioavailability and to extend the drug release up to 20 hours and to compare with that of reference standard. Venlafaxine hydrochloride is widely used antidepressant drug belonging to chemical category of serotonin-nor-epinephrine-dopamine reuptake inhibitor. Venlafaxine hydrochloride belongs to BCS Class I drug having high solubility and high permeability, it has short elimination of half life of 5±2 hours and its daily dose is 225 mg/day, administered twice or thrice leads to chances of missing the dose in case of geriatrics. Hence, this research focused on developing the extended release drug delivery systems of venlafaxine by retarding the release rate of drug based on dissolution, diffusion or a combination of both mechanisms. In this type of dosage forms, a sufficient amount of drug is initially made available to the body to produce a desired

pharmacological response and the remaining fraction is released over a prolonged period, over which the maximum initial pharmacological activity is maintained. The novel system of drug delivery offers a means of improving the therapeutic effectiveness of the drug. Extended release pellets of venlafaxine employing different polymers of different ratios were prepared using ethylcellulose N-50, eudragit NE 30D, eudragit L100 55, and surelease as extended release polymers using drug layering solution method by Pelletization technique.[5, 6]

MATERIALS AND METHODS

Materials

Venlafaxine Hydrochloride was a gift sample from Ra chem Laboratories, Hyderabad, Sugar Spheres#20 from Meghana labs, Hyderabad, Aerosol, Hypromellose from Sigma Aldrich, Bangalore, Eudragit, Surelease from Basf, Germany, Ethyl cellulose from Feichein, Poly Ethylene Gylcol-6000 from Clarient, Magnesium stearate from Sigma Aldrich labs, Bangalore, and Isopropyl Alcohol from Rankem laboratories were used under pharmacopoeial grade.

METHODS

Formulation of Venlafaxine HCl ER Coated Pellets

Pulverize the venlafaxine HCl & sucrose through 0.5mm screen and collect the pulverized material into labeled double lined poylthene bag HDPE container. Sift the sucrose, aerosil, through #100 Vibro Sifter (Sartorius) and collect the material followed by transfer the pulverized and sifted material one by one in conta blender(Platinum Pharmatech) and then Blend the material about 15 min at 12 RPM.

In next step prepare the blending solution by taking of the purified water in container and add hypromellose, sucrose (syrup grade) in purified water under continuous stirring till the clear solution is obtained. Filter the clear solution through #200 nylon cloth into a cleaned container. And the further step is drug loading in this case load the sugar spheres (#22#24) taken into coating pan (Platinum Pharmatech(PPTC 18) and start the coating pan and allow the spheres to rotate. Adjust the spray gun atomization air pressure to 1.0-2.0 kg/sq cm, start the peristaltic pump and adjust to 5-15 RPM. Start spraying the syrup solution by maintaining the gun distance about 30- 40cm, continues spraying till the spheres becomes wet. Add drug blend in small quantities to the wet pellets in the coating pan until the spheres are free flowing. Adjust the peristaltic pump 15-40 RPM and continue the spraying of syrup solution and powder addition till the complete drug free flowing. Adjust the peristaltic pump 15-40

RPM and continue the spraying of syrup solution and powder addition till the complete drug blend is exhausted.[7]

After completion of the process unload the wet drug pellets into trays in equal quantities and keep for drying in tray dryer (Millennium Equipments Pvt Ltd (METD-6G). Load the wet coated pellets into tray drier and load the trays into drier. Set the inlet temperature at 45±3ºC and maintain the bed temperature between 42º- 48ºc. Sift the dried pellets through #16 and collect 16# retained and passing separately into the poly bag. Sift #16 passing pellets through #20 and collect retains and passing separately into poly bag. The sifted pellets are collected into HDPE containers.

Drug-Excipient Compatibility Study

Fourier Transform Infrared (FTIR) Studies

Fourier Transform Infrared Spectrum of pure drug and sample containing the drug in combination with optimized concentration of polymer were recorded using FTIR Spectrophotometer in the scanning range of 500 to 4000 cm-1 as show in Figure 1 & 2. From the results obtained it was found that there is no possible chemical interaction is present with the drug from formulation.

Differential Scanning Calorimetry

Thermal analysis of the samples containing the drug and blend of optimized formulation were carried out with a DSC Q200 Model (TA Instruments). About 2-5 mg of samples were sealed into aluminium pans and scanned at a heating rate of 10°C/minute over a temperature range of 50-250°C under a nitrogen gas stream. The DSC thermograms are shown in Figure 3-4.

Estimation of venlafaxine HCl

An ultraviolet (UV) spectrophotometric method based on the measurement of absorbance at 226nm was used for the estimation of venlafaxine hydrochloride by using UV – visible spectrophotometer (Shimadzu UV – 1601, Japan). The standard curve of venlafaxine Hydrohloride in pH 6.8 phosphate buffer were shown in Table 2. The method obeyed Beers-lambert's law in the concentration range of 0 – 20 (µ/ml). And the Characterization of active pharmaceutical ingredient and polymer was performed. For that purpose Fourier Transform Infra Red Spectroscopy was used and the thermal analysis for characterizing interaction between drug and excipients.

Extended Release Coating for the Drug Loaded Pellets[8]

Preparation of Coating Solution

Coating solution for the preparation of ER pellets were prepared by passing the isopropyl alcohol (IPA) through #200 nylon cloths into the container and dissolve, half quantity of the Ethyl cellulose in IPA with continuous stirring for about 15 min. Dissolve the polyethylene glycol 6000 in purified water with continuous stirring in a separate container. Mix the above prepared solution with magnesium stearate and PEG 6000 solution to Ethyl cellulose, continue this stirring for 15 min. After stirring, filter the solution through #200 nylon cloth into separate containers.

Coating Process

Load the drug coated pellets into the product bowl and carry out the operation as pre standard operating procedures. Set the inlet temperature to 45º- 60ºc & maintain the bed temperature between 38º- 44ºc by adjusting the inlet set temperature. Coat the drug pellets by bottom spray Wurster at peristaltic pump RPM of 25-100 and atomizing air pressure of 3.0-5.0 Kg/cm^2 till the coating solution is completed. After completion of solution, dry the pellets in FBC for about 15 minutes at given bed temperature & Atomization air pressure 3.0kgs/cm^2. Collect the coated pellets from the container and sift th**e** Ethyl cellulose coated pellets through #16 and collect pellets and store below 25ºc. Collect sifted Venlafaxine HCl in HDPE Containers lined with virgin double poly bags and stored at below 25℃.

To evaluate the individual and combined effects of different polymers on the buoyancy and drug release characteristics, the ER pellets were formulated using selected polymers by following the above same procedure as the formulae given in Table 1.

Evaluation of Extended Release Pellets[9]

The Prepared coated pellets were evaluated for different quality control tests like bulk density, compressibility index and Hausner's ratio, angle of repose, friability, weight variation, and disintegration tests.

Bulk and Tapped Density

Accurate quantity of pellets was weighed, transferred into the graduated cylinder and volume of pellets in the cylinder was measured as V_0. The graduated cylinder was fitted with the lid and kept in the tapped density tester (USP) and it was operated to run for 100 taps, finally the

volume of pellets in the cylinder measured as V_f. The bulk density, and tapped density were calculated using the following formula.

Bulk density = W / V_o

Tapped density = W / V_f

Where,

W = weight of the powder

V_o = initial volume

V_f = final volume

Compressibility Index

Compressibility index/Carr's index is indirectly related to the relative flow rate, cohesiveness and particle size of a powder and is calculated from the bulk density and tapped density values using the following formula.

$$\text{Compressibility index} = \frac{\text{T.D}-\text{B.D}}{\text{T.D}} \text{x}100$$

Hausner's Ratio

It indicates the flow property of the powder and measured by the ratio of tapped density to bulk density. Value of this ratio less than 1.25 indicates good flow characteristics which is equivalent to the 20% of carr's index.

$$\text{Hausner's ratio} = \frac{\text{T.D}}{\text{B.D}}$$

Where, T.D= Tapped density, B.D= Bulk density.

Angle of Repose

The flow characteristics of pellets are measured by angle of repose. Improper flow of particles is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$$\tan Q = \frac{\text{h}}{\text{r}}$$

Where,

h = height of pile

r = radius of the base of pile.

Q = angle of repose.

Friability Test

10 grams of pellets were accurately weighed and transferred to friability test apparatus (Roche friabilator) which was operated at 25 rpm for 4 minutes and pellets observed while rotating. The pellets were then taken out after 100 rotations, the weight of pellets was recorded after removing fines using sieve #44. Friability values below 0.8% are generally acceptable.

% Friability = (W1 – W2) x 100/W1

Where,

W1 = Initial weight of the 20 tablets.

W2 = Final weight of the 20 tablets after testing.

***In vitro* Disintegration test**

The test for disintegration time of pellets was determined using thermonic disintegration test apparatus using pH 6.8 phosphate buffer. The accurately weighed quantity of pellets equivalent to 50 mg of drug were filled into the capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºc ±5ºc and observed over the time described in the individual monograph.

Particle Size Distribution

100gms of pellets were accurately weighed and shifted into a sieve shaker where a series of sieves was placed in the order of 16#, 22#, 25# and 30#. The machine was run for 5 minutes, all the sieved were taken out and retained granules collected by respective sieve and the percentage retention of pellets and the data was tabulated in table 4.

Scanning Electron Microscopy

Surface morphology of the extended release coated pellets of venlafaxine hydrochloride was analyzed using scanning electron microscope. Prior to the examination, samples were fixed on a brass stub using double-sided adhesive tape and then gold coated in vacuum by a sputter coater. The SEM photographs were taken at an excitation voltage of 10 KV and are shown in Figure 6.

In Vitro Drug Release Study[10]

In vitro dissolution rate of venlafaxine hydrochloride extended release pellets was carried out using 8 station USP Type II dissolution test apparatus (Electro lab (ED- 2AL, Mumbai). The dissolution rate of pellets equivalent to 33 mg of venlafaxine hydrochloride was studied in 900 ml of pH 6.8 phosphate buffer at a speed of 50 rpm and a temperature of 37±0.5°C up to 20 hours. Samples of dissolution medium (5ml) are withdrawn at different time intervals 0, 2, 6, 8, 10, 12, 18, 20 hours through 0.45µ nylon disc filtered, suitably diluted and assayed for venlafaxine hydrochloride by measuring absorbance at 226nm. The dissolution experiments were conducted in triplicate and the values are reported in table 5 and comparison of dissolution profiles shown in figure 5 for twenty hours.

Kinetic Modeling Data Analysis

In vitro drug release data was analyzed as per zero order, first order, higuchi and pepas equation models to assess the drug release kinetics and mechanism of the drug release from the capsules prepared.

RESULTS AND DISCUSSION

In the present work Extended release capsules each containing 33 mg of venlafaxine hydrochloride multiparticulate systems were prepared using solution laying method by pelletization technique. The wavelength maxima for venlafaxine hydrochloride is determined at 226 nm using UV spectrophotometric method of analysis and the calibration curved was plotted in pH 6.8 phosphate buffer found to obey the Beer's-Lamberts law within the range of 0-20µg/ml concentration of drug solutions. The drug-exipient compatibility studies also performed using the Fourier Transform Infra Red spectrophotometer (FTIR) and differential Scanning Calorimeter (DSC) for drug and sample containing the drug and optimized concentration of polymer showed the similar spectra reveals that there is no possible chemical interaction and hence the drug is compatible with the polymers used in the formulation. Physical properties of drug and raw materials were performed and are found to be within the limits.

The micromeritic properties such as bulk density, tapped density, angle of repose, hausner's ratio, and Compressibility index were studied. The angle of repose of all the formulations ranges from 32.6^{o} – 29.87^{o} which depicts excellent flow characteristics. Bulk density ranges from 0.628 gm/ml-0.66gm/ml. Tapped density for the coated formulations lies between 0.778gm/ml-0.703 gm/ml. Hausner's ratio of all coated pellet formulations ranges from

1.23gm/ml-1.06 m/ml. The values of compressibility index show that all the values were found to be within limits and exhibits excellent flow character. The overall results were tabulated in table 3. Results of the drug content analysis showed all the formulations contain 100% of the labeled claim of Venlafaxine Hydrochloride. The friability for coated pellets were checked and it ranges from 0.214-0.965% w/w and the values depicts friability is within IP limit which is not more than 1% w/w, indicating the sufficient mechanical integrity and strength of prepared pellets.

In this experiment Eight formulations of venlafaxine extended release pellets were prepared by solution laying using sugar spheres used as core material, sucrose as a diluent, Colloidal Silicon dioxide used as glidant, hypromellose is as binder, Ethyl cellulose N-50, Eudragit NE 30D, Eudragit L100 55 and Surelease were used as release rate retarding polymers, Polyethylene glycol 6000 as plasticizer and Magnesium stearate used as lubricant. The weight loss in the friability test was less than 0.965% in all cases. Standard plot of Venlafaxine Hydrochloride in pH 6.8 phosphate buffer solution was performed and was found to obey the beer's-lamberts' law within the range of 0-20µg/ml and the values are given in the Table 2. The *in vitro* disintegration profile for the above formulations were conducted and were tabulated in the table 3 and the dissolution profiles of ER coated pellets of venlafaxin HCl (F1-F8) were given in the table 5.

From the above results it was found that, the formulation F1 coated pellets with 5% w/v of Eudragit NE 30D (independent) produced 91.1% of release in buffer medium and also it is in continued with indiscriminate medium. So, the formulation F2 was coated with 10% Eudragit and this coating results in fast drug releasing within 10 hours in buffer medium. By observing the previous trails, than decided to take pH dependent polymer like Eudragit L100 55 as it is soluble in pH 6-7, as we have our official medium is also with in this range. In the formulation F4, 95.8% of drug released, the result was improved when compared with F1 & F2. But in this trail the polymer has changed because as our reference product shows pH independent release profile so that, we decided to the use of pH independent polymer. Hence formulation F5 was tried with 3.13% of surelease as rate retarding polymer and the acquired result was 83.1% of venlafaxine HCl released at the end of 20 hours. As above results were not satisfactory, surelease retarding the release of Venlafaxine HCl in buffer medium when compared with the other formulation. So, the alternate coating polymer ethylcelluolse N-50 was decided to apply in the further formulation.

Formulation F4 was coated with 9.0% of surelease to the core pellets and the result was obtained as 96.6%. To retard the drug release more than the formulation F4 the concentration of surelease has been increased. To retard the drug release with ethylcelluolse the concentration was decided to take equal to (or) less than the concentration of surelease. Hence, formulation F6 & F7 was tried with 5.13% & 7.13% of drug was released and observed to produce within the desired range in phosphate buffer & the optimized batch was taken with ethylcelluolse.

From the above observations, formulation F1 to F4 does not complies with desired drug release retard in the phosphate buffer medium and the continuous buffer stage dissolution was performed but not satisfactory. Formulation F5 and F6 had a better drug retarding property so the process was carried to next continuous pH 6.8 phosphate buffer stage for 20 hours. F6 & F7 showed the good extended release characteristics when compared with that of F1 to F4.

When compared to F7, formulation F8 has shown good release tendency like the reference product. From the overall results suggest that the release profile of both F7 & F8 both these trails were taken for the indiscriminate medium analysis, but the formulation F8 showed good release data hence it was optimized as the best formulation among all batches.

The *invitro* dissolution data were fitted into various mathematical models such as zero order, first order and higuchi models to assess the kinetics and mechanism of drug dissolution. All the formulations found to obey the first order kinetics and the drug release is through diffusion controlled since the values of correlation coefficient nearer to 1.0.

Scanning electron micrograph of core and coated pellets describes the surface morphology of pellets indicating the smooth surface of the drug coat on the base pellets because of optimization of concentration of polymer required to coat the base pellets to produce the desired release profiles size of coated pellets ranges from 825µm to 1050µm. with mean particle size of 960µm.

The stability of the pellets was determined by conducting “Accelerated stability testing” in 40°C ± 2°C / 75% ± 5%RH, 25ºC ± 2 ºC/ 60% RH ± 5% RH, and 30ºC±2ºC/65±5% RH conditions for 3 months as per ICH guidelines in HDPE containers. Finally after the duration, the product was analyzed for weight variation, content uniformity, and assay and dissolution

studies. Since there is no difference in the physical appearance and the values obtained from the stability studies, the formulated venlafaxine hydrochloride extended release pellets were proved to be stable throughout the period of the storage.

Table 1: Formulae for the Preparation of Venlafaxine HCl Extended Release (ER) Pellets.

S.No	Name of Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
1	Venlafaxine Hydrochloride	33	33	33	33	33	33	33	33
2	Sugar Pellets (#20#24)	40	40	40	40	40	40	40	40
3	Aerosil	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
4	Sucrose	12.02	11.52	15.02	16.86	12.52	14.66	12.66	9.80
	Binder solution								
5	Sucrose	3.00	3.00	3.00	3.00	3.00	3.00	3.20	3.20
6	Hypromellose (HPMC 606)	0.38	0.38	0.38	0.38	0.38	0.38	0.38	0.38
7	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	ER Coating								
8	Eudragit NE 30D	5	10	-	-	-	-	-	-
9	Eudragit L100 55(dependent)	-	-	6	-	-	-	-	-
11	Surelease Independent	-	-	-	3.13	9	-	-	-
12	Ethyl Cellulose N-50	-	-	-	-	-	8.02	7.13	10.0
13	Polyethylelne Glycol-6000	1.0	0.5	1	0.34	0.5	0.34	0.34	0.34
14	Magnesium Stearate	4	1	1	2.69	1	1.64	2.69	2.68
15	Isopropyl alcohol	Q.S	-	-	-	-	-	Q.S	Q.S
16	Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight (mg)		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Table 2: Calibration Curve of Venlafaxine Hydrochloride in pH 6.8 Phosphate Buffer.

S.NO	Concentration (µg/ml)	Absorbance Mean Value at 226nm	% RSD
1	0	0.0000	0.54
2	4	0.1992	0.61
3	6	0.3197	0.39
4	8	0.4104	0.57
5	12	0.6035	0.83
6	16	0.8021	0.42
7	20	0.9438	0.91

Table 3: Physicochemical Properties of Venlafaxine Hydro Chloride ER pellets*:*

S.No	Parameters	F1	F2	F3	F4	F5	F6	F7	F8
1	Disintegration time (min)	4.50	4.40	5.10	4.50	4.50	4.55	5.05	4.25
2	Angle of Repose (degrees)	32.6	29.0	31.8	27.84	27.8	28.4	28.32	29.87
3	Bulk Density (gm/ml)	0.628	0.621	0.614	0.614	0.655	0.694	0.702	0.66
4	Tapped Density (gm/ml)	0.778	0.728	0.712	0.712	0.742	0.785	0.790	0.703
5	Compressibility Index (%)	19.2	14.6	13.7	13.06	11.7	11.5	11.1	6.11
6	Hausner's Ratio	1.23	1.17	1.15	1.15	1.13	1.13	1.12	1.06
7	Loss on Drying (%)	2.05	1.75	2.25	2.10	2.08	0.99	0.97	0.85
8	Friability (%)	0.214	0.175	0.326	0.563	0.459	0.523	0.143	0.965
9	Drug Content (%)	100.56	96.75	98.78	99.04	99.86	99.9	100.01	100.02

Table 4: Sieve Analysis of Venlafaxine Hydro Chloride ER Capsules (F1-F8)

S.No	Sieve No	Percentage of Sample Retained In Each Sieve (%)							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	16 #	9.1	10.9	11.2	12.4	13.4	11.8	12.4	12.6
2.	20 #	20.9	29.1	29.0	30.4	42.8	46.3	52.2	52.2
3.	24 #	70.0	60.0	60.8	57.2	43.8	41.9	35.4	35.2

Table 5: Comparative Dissolution profile of Venlafaxine ER Pellet Formulations (F1-F8) with Marketed Product (Effexor)

S.No	Time in hrs	Cumulative Percent Drug Released (Mean ±SD) n=3								
		Effexor 75mg	F1	F2	F3	F4	F5	F6	F7	F8
1	0	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00	00.0±0.00
2	2	14.2±0.11	13.6±0.55	33.6±0.18	11.2±0.53	10.2±0.72	22.3±0.84	19.5±0.82	12.6±0.66	10.2±0.36
3	6	42.6±0.28	22.7±0.92	55.3±0.27	39.2±0.84	21.2±0.33	42.1±1.45	35.3±0.71	23.6±1.52	24.9±0.46
4	8	60.2±0.64	46.9±0.63	75.6±0.54	55.4±0.37	32.1±0.52	56.9±0.63	52.35±0.90	47.8±0.66	33.5±0.38
5	10	73.7±1.02	67.6±0.41	86.4±0.66	73.2±0.81	60.3±0.98	72.6±0.58	70.45±0.60	68.3±0.41	62.9±0.44
6	12	81.4±0.85	76.1±0.98	98.9±0.71	82.6±1.34	69.6±0.85	79.7±0.38	78.9±0.46	78.1±0.60	79.8±0.42
7	18	90.4±0.38	81.3±0.83	98.9±0.74	90.6±0.48	76.6±0.26	87.4±0.65	85.3±1.2	83.2±0.90	85.5±0.16
8	20	97.8±0.57	91.1±1.26	98.9±0.85	95.8±0.51	83.1±0.55	96.6±0.79	95.3±0.94	94.6±0.46	96.2±0.82

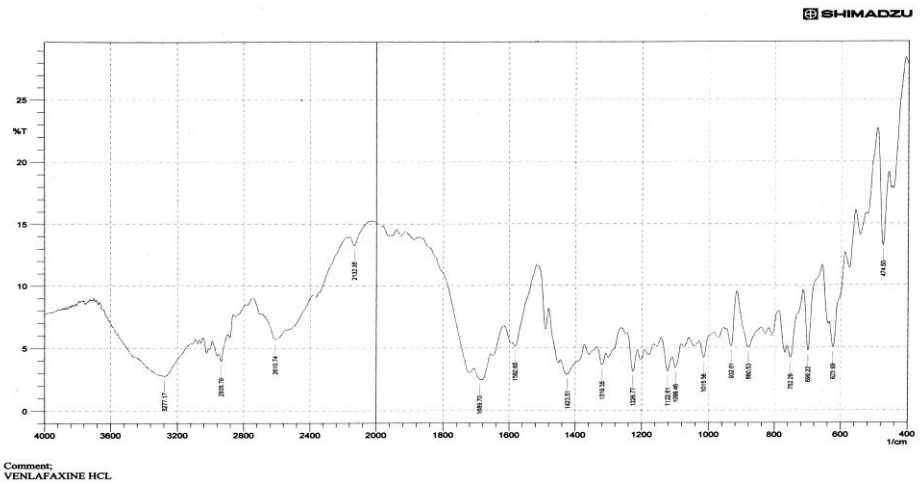

Figure 1: FT-IR Spectra of Venlafaxine HCl (Pure Drug).

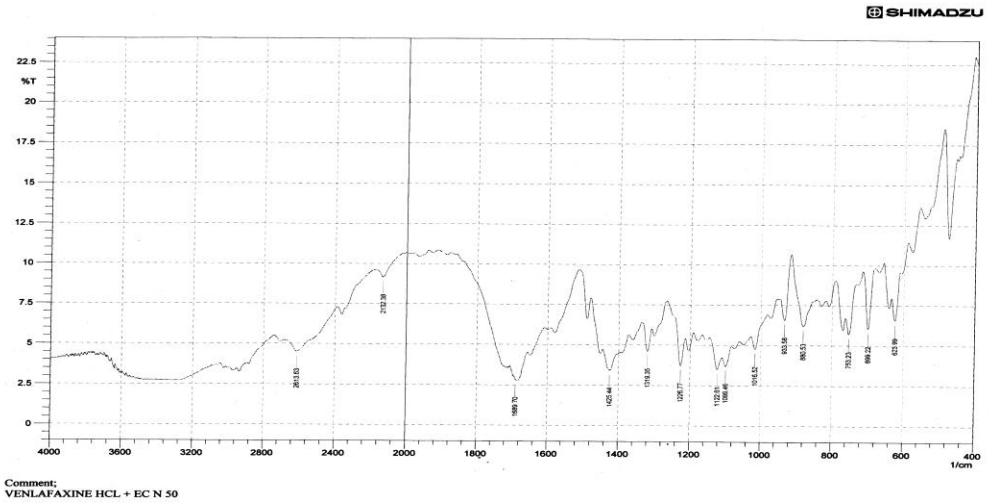

Figure 2: FT-IR Spectra of Venlafaxine HCl ER Coated Pellets (F8) Optimized Formulation containing EC- N50.

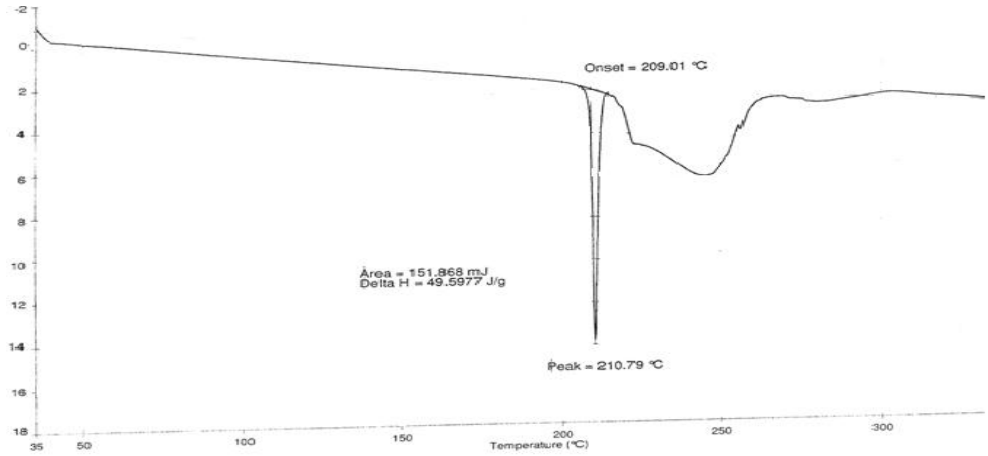

Figure 3: DSC Thermogram of Venlafaxine HCl (Pure Drug).

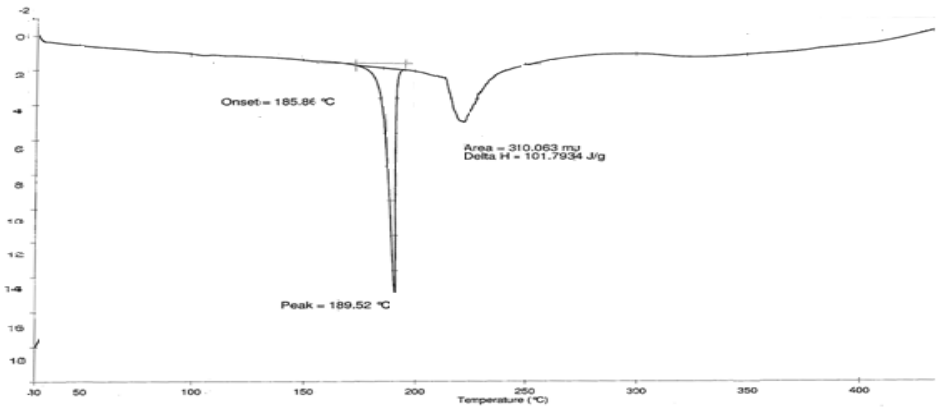

Figure 4: DSC Thermogram of Venlafaxine HCl ER Coated Pellets (F8) Optimized Formulation containing EC- N50.

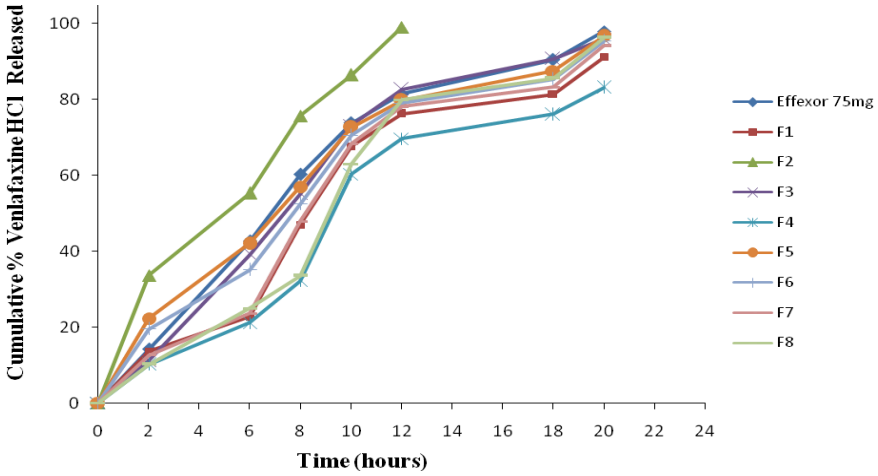

Figure 5: Comparative In vitro Dissolution Profile of Venlafaxine HCl ER Pellet Formulations (F1- F8) with Reference Product (Effexor).

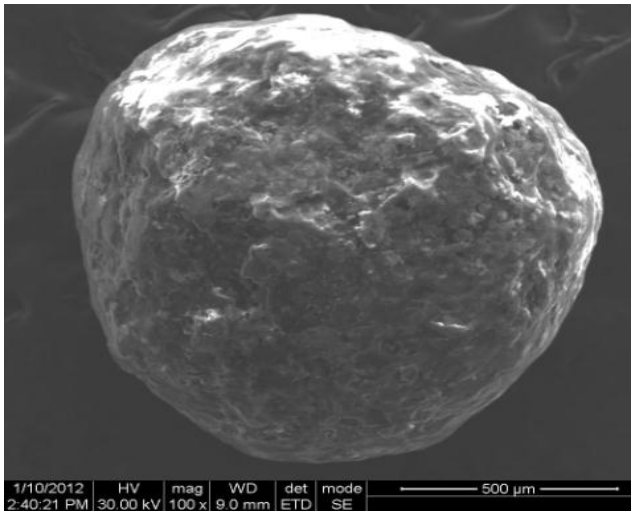

Figure 6: SEM (Scanning Electron Microscope) Micrograph of Optimized Pellet Formulation F8 after 90 Days of Accelerated Stability Studies.

CONCLUSIONS

Venlafaxine hydrochloride was subjected to preformulation studies, which encompasses the drug-excipient compatibility study using the FTIR Spectroscopy and Differential Scanning Calorimeter and the results obtained with selected excipients showed good compatibility with Venlafaxine Hydrochloride drug. Different evaluation tests and micromertitic studies were conducted and were found to be satisfactory.

Venlafaxine Hydrochloride coated pellets were formulated by using commercially available dummy sugar pellets and various release rate retardant required producing the desired

extended release of the drug to 20 hours. The quantity equivalent to 75 mg of venlafaxine hydrochloride ER coated pellets was filled into capsules by automatic capsule filling machine. The optimization procedures aided in the stabilization of the formula and in comparison with the formulation of the venlafaxine hydrochloride modified release capsules. The *invitro* drug release in the starting hours is controlled by increasing the concentration of Ethyl cellulose N-50 in the formulations in F7 formula and the plasticizer is also increased It was observed that the release profile of drug from the pellets was good by using ethyl cellulose polymer, when compared with the Eudragit NE 30 D (independent), Eudragit (dependent) L100 55 & Surelease and hence the dissolution profiles of coated pellets reveals that the concentration and type of polymer are having great importance in optimizing the formulation.

Stability studies were conducted for optimized formulation F8 at different conditions of temperature and relative humidity for about 3 months and formulation was evaluated for different physicochemical parameters before and after the storage period. The results Invitro dissolutions studies and physicochemical parameters reveal that there is no significant change obtained in the formulation during storage period.

The Venlafaxine Hydrochloride extended release pellets were loaded in size 1 hard gelatin capsules. It showed good results in formulation of stable dosage. The dissolution profile of the prepared Venlafaxine Hydrochloride extended release capsules were compared with that Venlafaxine Hydrochloride modified release capsules (Effexor) of the product. The release was found similar to that of innovator. So the prepared product was said to be equivalent with innovator.

When coated pellets in capsule come to discussion of dosage form extended release pellets showed better drug release which has minimum volume in size, greater surface area and more surface activity. The area of the drug loaded pellets release rate was also more. Because of Small size, pellets enter into the systemic circulation in very fast. Moreover there was no accumulation of drug in the body and hence drug release rate was more.

Overall results, it was observed that the venlafaxine extended release pellets of formulation F8 has relevant and desired drug release rate than the formulations containing other release rate retarding polymers, it has better stability, and would show the better bioavailability.

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