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Formulation and evaluation of extended-release tablets of an antidepressant drug Venlafaxine HCl

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ABSTRACT

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form is extended-release dosage form. It includes controlled-release, sustained-release, and long-acting drug products. The mechanism of action of venlafaxine HCl in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-Desmethylvenlafaxine (ODV), inhibit the reuptake of both serotonin and norepinephrine. In the present work, an attempt has been made to develop extended-release (ER) coated tablets of Venlafaxine HCl by selecting different grades of polymers, Hydroxypropyl methyl cellulose, ethyl cellulose and xanthan gum. These are used as retarding polymers to extend the drug release. All the formulations were prepared by wet granulation method and compressed using 9.8 mm punches on 16 stations rotary tablet punching machine. The blend of all the formulations showed poor flow properties. In order to improve flow, higher % of glidant was used. The coating material used was ethylcellulose aqueous dispersion (Aquacoat ECD 30). The prepared ER coated tablets of Venlafaxine HCl showed good post-compression parameters. They passed all the evaluation tests as per USP limits. Among all the formulations, F7 showed maximum % drug release, i.e., 99 % in 24 hours hence it is considered as optimised formulation. The optimised formulation compared with marketed tablets.

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of the different dosage form. The oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process (Ansel, 2004).

Extended-release drug products (Jain, 2008) are dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release dosage form.

Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

The US FDA defines sustained release dosage form as one that allows a reduction in dosing frequency from that necessitated by a conventional dosage form, such as a solution or an immediate release dosage form. (Banker, 1996; Yie, 1991; Leon, 2005)

In erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, the formation of the gel layer and its dynamics as a function of time determines the drug release. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate. The design of the extended-release delivery system is subjected to several variables of considerable importance. Among these, properties of the drug, the route of delivery and the disease treated and length of the therapy have major importance.

The mechanism of action of venlafaxine HCl in humans is believed to be associated with its potentiation of neurotransmitter activity in the Central Nervous System. Venlafaxine and its active metabolite, O-Desmethyl venlafaxine (ODV), inhibit the reuptake of both serotonin and norepinephrine with a potency greater for the 5-Hydroxy Tryptamine than for the Norepinephrine reuptake process. Both venlafaxine and the ODV metabolite have weak inhibitory effects on the reuptake of dopamine.

MATERIALS AND METHODS

The excipients used for wet granulation, pre-lubrication and extra granulation were Povidone 90 (Signet Chemicals Corp. Pvt. Ltd.), HPMC K 100M & HPMC K200M DC2 (Colorcon Pvt. Ltd.), Ethylcellulose 100 cps (Colorcon Pvt. Ltd.), Aerosil (Waker Chemic AG), Magnesium stearate (Peter Greven) & Talc (Signet Chemicals Corp. Pvt. Ltd.). The ingredients used for extended release coating includes Aqua coat ECD 30 (Signet Chemicals Corp. Pvt. Ltd.), HPMC (Colorcon Pvt. Ltd.) and Dibutyl sebacate (Vertellus Performance materials). Opadry white (Colorcon Pvt. Ltd.) was used for film coating of venlafaxine HCl (Alembic Pharmaceuticals) extended-release coated tablets.

Electronic balance (Sartorius: BSA423S-CW), Rapid Mixer Granulator (Saral India Pvt. Ltd.), Moisture Analyzer (Sartorius MA 100), Fluidized bed drier (Retsch TG 200), Co-Mill (Quadro-Co-Mill), Octagonal blender (SAAN Pvt. Ltd.), Tablet Compression machine (CADMACH CMD4 Rotary Tablet Press), Digital Vernier Caliper (Mitutoyo Digital Vernier caliper), Tablet hardness tester (Pharmatron Tablet tester), Friability test apparatus (Electrolab Friability Apparatus USP), Coating Machine (Gansons coater) and Dissolution test apparatus (Lab India Dissolution Apparatus Ds 8000(USP)).

Preformulation studies

Preformulation studies were performed to investigate the physical and chemical properties of a drug substance alone and also when combined with other substances such as excipients (Lachman, 1986).

Physical characteristics

Loss on drying

About 1gm of Venlafaxine HCl was placed in the plate of the digital moisture balance instrument. The temperature was set to 105°C, and the instrument was run till a constant weight was obtained. Finally, the percentage loss on drying was read out automatically on the panel.

Solubility Studies

Solubility study was performed at room temperature or ambient temperature. 100 ml of solvent or medium was taken into 100 ml volumetric flask in which 100 mg of Venlafaxine HCl was added. After handshaking for 15 min, the solution was ultrasonicated until the material was completely dissolved. The solution was filtered through a 0.45 μm filter to get a clear solution. The filtered solution was diluted to get a concentration approximately equal to that of a standard preparation. The content of Venlafaxine HCl was estimated by U.V. method (Venkateshwarlu, 2004).

Flow properties

The flow properties of powders are critical for an efficient tabletting operation. If a drug is identified to be "poorly flowable" at the preformulation stage, the problem can be solved by selecting appropriate excipients (USP, 2007; Staniforth, 2002).

Bulk density

Bulk density is determined by pouring the pre-sieved powder into a graduated cylinder via a large funnel and measuring its volume and weight (USP, 2007b).

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Bulk volume}}$$

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of powder on a mechanical tapper apparatus, which

Table 1: Composition of Venlafaxine HCl tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Venlafaxine HCl	169.72	169.72	169.72	169.72	169.72	169.72	169.72	169.72
Microcrystalline cellu- lose	60.28	50.28	62.28	42.28	42.28	82.28	82.28	82.28
Lactose monohydrate	20.00	20.00	-	-	-	-	-	-
Povidone 90	40.00	40.00	-	20.00	20.00	-	-	-
Xanthan gum	72.00	72.00	-	-	-	-	-	-
HPMC K100M	-	-	160.00	-	-	100.00	100.00	40.00
Ethylcellulose 20 cps	-	-	-	-	-	40.00	-	-
Ethylcellulose 100 cps	-	-	-	-	-	-	40.00	100.00

Table 2: Precompression data of various formulations

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio
F1	0.490 ± 0.020	0.65 ± 0.025	24.61 ± 1.5	1.32 ± 0.10
F2	0.512 ± 0.018	0.71 ± 0.018	28.04 ± 1.0	1.39 ± 0.06
F3	0.300 ± 0.030	0.42 ± 0.030	30.00 ± 1.2	1.42 ± 0.08
F4	0.320 ± 0.022	0.46 ± 0.022	30.43 ± 2.0	1.43 ± 0.04
F5	0.372 ± 0.019	0.56 ± 0.029	33.84 ± 1.6	1.51 ± 0.12
F6	0.370 ± 0.031	0.53 ± 0.035	30.18 ± 2.0	1.43 ± 0.08
F7	0.340 ± 0.027	0.51 ± 0.029	33.33 ± 1.0	1.50 ± 0.09
F8	0.360 ± 0.020	0.53 ± 0.027	32.07 ± 0.5	1.47 ± 0.07

is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed (USP, 2007b).

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

Carr's index

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find Carr's index (Davies, 2004).

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

The Hausner's ratio indicates the flowability and packing ability of the tablet. When the Hausner's ratio is close to 1, materials have adequate flow and packing ability (Davies, 2004). Hausner's Ratio was calculated using the formula:

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

Drug-excipient physical compatibility studies

Drug and excipient are mixed in different ratios and mixed in a polythene bag for 5 min. Each mixture is allotted sample code for identification and the mixtures are thoroughly sealed in glass vials and exposed to different temperature and humidity conditions (40 ± 2°C & 75 ± 5% RH). The study was conducted for 1 month and the drug excipient

blends were evaluated for physical appearance. Samples kept at a temperature of 2-8 ^{0}C (refrigerator) were considered as controlled samples.

Formulation of Venlafaxine HCl Extended-Release Tablets

The Extended-release tablets containing 150 mg Venlafaxine HCl were prepared with a total tablet weight of 457 mg. (Table 1)

Preparation of Venlafaxine HCl Tablets

Wet granulation

Venlafaxine HCl, Avicel PH 101, Methocel K100M CR, Ethylcellulose 10cps, was sifted through sieve # 30 ASTM. These ingredients were loaded into Rapid Mixer Granulator (RMG) and mixing it with impeller and chopper at a slow rate. Fluid uptake was 60% w/w. Povidone 90 (F4 & F5), Iso Propyl alcohol (F3, F4, and F5), Purified water (F2, F3, F4, and F5) and ethanol (F1, F6, F7 and F8) were used as granulating agents. Binder was added at an impeller speed of 150 RPM for 5 min and then kneading was done for 2 min at same impeller speed but at slow chopper speed. The wet mass was loaded in Rapid drier at 60°C±5°C to achieve LOD NMT 3% w/w Sifting and Milling. Then the dried granules were passed through sieve # 25 ASTM and the granules retained on sieve # 25 were milled in Quadro- co-mill (slow speed). The process for milling was repeated until all the granules passed through sieve # 25.

Table 3: Evaluation parameters of core tablets

Formulation code	Thickness (mm) n=10	Hardness (KP) n=10	Friability (%w/w) n=20	% Drug content
F1	6.01 ± 0.02	8.01 ± 1.2	0.0303 ± 0.002	96.19
F2	5.75 ± 0.06	8.69 ± 1.3	0.0305 ± 0.003	99.69
F3	6.24 ± 0.01	7.90 ± 1.0	0.0501 ± 0.005	99.77
F4	6.06 ± 0.02	9.11 ± 0.8	0.0391± 0.003	100.38
F5	5.93 ± 0.02	11.4 ± 0.8	0.0297 ± 0.006	99.38
F6	6.04 ± 0.04	9.17 ± 1.2	0.0315 ± 0.005	96.5
F7	5.92 ± 0.08	9.57 ± 1.6	0.0600 ± 0.003	99.49
F8	5.97 ± 0.05	7.99 ± 2.0	0.0505 ± 0.003	98.17

Table 4: Evaluation parameters of coated tablets

Formulation code	Thickness (mm) n=10	Hardness (KP) n=10	Friability (%w/w) n=20
F1	6.09 ± 0.02	11.9 ± 1.0	0.0325 ± 0.002
F2	6.15 ± 0.06	13.52 ± 0.2	0.0511 ± 0.003
F3	6.67 ± 0.02	10.45 ± 1.2	0.0381 ± 0.002
F4	6.64 ± 0.01	10.84 ± 1.6	0.0287 ± 0.006
F5	6.36 ± 0.02	14.01 ± 0.4	0.0295 ± 0.004
F6	6.36 ± 0.02	14.03 ± 0.6	0.0303 ± 0.005
F7	6.37 ± 0.04	12.54 ± 0.2	0.0305 ± 0.004
F8	6.48 ± 0.02	11.26 ± 1.2	0.0605 ± 0.002

Table 5: Correlation Coefficient (R2) values for marketed and F7 formulation

Release kinetics	Marketed Formulation		ER venlafaxine HCl (F7)	
	Correlation Coefficient R^2	Diffusional exponent 'n'	Correlation Coefficient R^2	Diffusional exponent 'n'
Zero-order	0.991	-	0.992	-
First order	0.647	-	0.658	-
Higuchi	0.955	-	0.956	-
Korsmeyer peppas	0.811	1.048	0.811	1.048

Table 6: Stability study data (accelerated) of F7

S.No.	Parameters	Specifications	Test Condition (Accelerated) 40 ± 2°C & 75 ± 5% RH			
			0 Day	1 Month	2 Month	3 Month
1	Description	Extended-release coated tablet	Comply	Comply	Comply	Comply
2	LOD	Not more than 2.0%	1.427%	1.326%	1.211%	1.143
3	Assay	NLS 90% & NMT 110% of the labelled amount of drug.	100.9%	99.2%	99.3%	99.5%

Pre-lubrication & Extra granulation

Talc was sifted through ASTM # 40 mesh. Dried material and colloidal silicon dioxide were mixed in an octagonal blender for 10 min for Pre lubrication. Magnesium stearate was sifted through ASTM # 60 mesh. Colloidal silicon dioxide and Magnesium stearate were mixed in an octagonal blender for 10 min for lubrication. Extra granulation was done using HPMC K200M, HPMC K100M DC2, Ethylcellulose 100 cps, aerosil, magnesium stearate and talc to get a weight of about 400 mg.

Compression

Compression of the lubricated blend was done by using 9.8 mm round standard concave punches, plain on both sides.

Extended-release coating

Extended-release coating: 12% weight gain, 15 % solids; Coating material used: Aquacoat ECD 30

Step 1: Accurately weighed quantity of Aquacoat ECD 30 (37.04 mg) and dibutyl sebacate (6.12 mg) was added with continuous stirring for 30 min.

Step 2: HPMC E5 LV (4.84 mg) was dissolved in purified water (q.s) under stirring.

Materials involved in Step 2 and step 1 were mixed with continuous stirring for 10 min. Extended-release coated tablets weight was about 448.00 mg.

The accurately weighed quantity of Opadry white (9 mg) was mixed with water under stirring for 10 min to get a total tablet weight of 457 mg.

Coating Parameters

The coating was done with dispersion strength of 12 %w/w at an initial drying temperature of 41 ℃. Initial load taken was 400 g with an initial drying time of 10 min. Coating pan and spray pan was revolved at 5 to 8 and 3 to 4 RPM respectively. Atomization was kept at 1.5 kg/cm^2 with an inlet temperature of 45 ℃. The product was maintained at 33 to 34 ℃ with a curing time of 30 min.

The coating was performed smoothly. No sticking of tablets was observed during the coating.

Evaluation of Tablets

Weight Variation Test

To study weight variation individual weights (W$_I$) of 20 tablets from each formulation were noted (Lachman, 1986). Percent weight variation was calculated as follows,

$$\% \text{ weight variation} = \frac{W_A - W_I}{W_A} \times 100$$

As the total tablet weight was 457 mg, according to USP, out of twenty tablets ±5 % variation can be allowed for not more than two tablets.

Hardness Test

10 tablets from each batch were selected and hardness was measured using tablet hardness tester. The hardness of 4 kg is considered suitable for handling the tablets.

Tablet Thickness

Thickness and diameter of formulation trials were measured using a Digital vernier Caliper & Thickness Gauge. 10 tablets of each trial formulation were taken and measured individually at frequent intervals.

Friability (%F)

Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in Friabilator after the given specification 100 revolutions (4 min at 25 RPM) (USP, 2010). The tablets were weighed again and % friability was then calculated by

$$\%F = \frac{W - W_V}{W} \times 100$$

Where,

% F =Friability of tablets in percent; W=Initial Wight of tablets, the W$_0$=Final weight of tablets.

Dissolution Test

900 ml of dissolution medium (purified water) was placed in the vessel and the temperature of the USP type II (Paddle) apparatus was adjusted to 37 ± 0.5 ℃. One tablet Venlafaxine HCl was transferred into each dissolution vessel. Immediately the apparatus was operated at the 50 RPM. At each of the time (1, 2, 4, 6, 8, 12, 16, 20 and 24 h) a sample volume was withdrawn. Replace the aliquots withdrawn for analysis with equal volumes of fresh dissolution medium at 37 ± 0.5°C. The vessel was kept covered for the duration of the test and verifies the temperature of the mixture under test at suitable times (Lachman, 1986).

Release Kinetics

Data of *in vitro* release was fitted into different equations to explain the release kinetics of Venlafaxine HCl extended-release capsules. The kinetic equations used were zero–order and first order equations (Paulo, 2001). The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero-order kinetic model – Cumulative % drug released versus time.

2. First – order kinetic model – Log cumulative percent drug remaining versus time.

3. Higuchi's model – Cumulative percent drug released versus square root of time.

4. Korsmeyer equation / Peppa's model – Log cumulative percent drug released versus log time.

Stability Studies

Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature, relative humidity etc. (Yoshioka et al., 1994). Accelerated stability studies on promising tablets were carried out by storing 15 tablets in rubber stopped vials at an elevated temperature of 40 ± 2°C/ 75 ±5 % RH (Stability chamber, Osworld) over a period of 3 months. After that, the tablets were visually examined for any physical changes, changes in drug content, assay and loss on drying.

RESULTS AND DISCUSSION

The present study was undertaken to formulate Venlafaxine HCl ER coated tablets. The study involves preformulation studies of drug and excipients, formulation and processing development along with an evaluation of tablets made with the optimized formulation. Finally, extended release coated tablets were evaluated by *in vitro* methods.

Physical Characterization of Active Pharmaceutical Ingredient (API)

API was a white crystalline powder which was soluble in water with a loss on drying value to be 2.0% maximum.

Solubility Studies

The solubility of Venlafaxine HCl drug was studied in six different media. The drug was found to be highly soluble in water (198.26 mg/ml) and also freely soluble in 0.1N HCl pH 1.2 (171 mg/ml), 0.01N HCl pH 2.1 (132.01 mg/ml), Acetate buffer pH 4.5 (48.45 mg/ml), phosphate buffer pH 6.8 (132.45 mg/ml) and phosphate buffer pH 7.2 (114.33 mg/ml).

Flow Properties

Bulk density (0.135 ± 0.30 g/ml), tapped density (0.253 ± 0.29 g/ml), Carr's index (46.26 ± 2 %) and Hausner's ratio (1.861 ± 0.06) were calculated for checking the flow property of the drug. The result indicates that the drug exhibit very poor flow as its nature was very fluffy. Hence to overcome the flow issue during compression 0.75%, extra Aerosil was added to formulation F7.

Drug - Excipient Physical Compatibility Studies

The drug and excipients compatibility test was performed and no change in colour was seen. The drug was found to be compatible with all the excipients (MCC, Lactose monohydrate, HPMC, Ethylcellulose, Aerosil, Magnesium stearate, povidone and Xanthan gum in the ratio of 1:1).
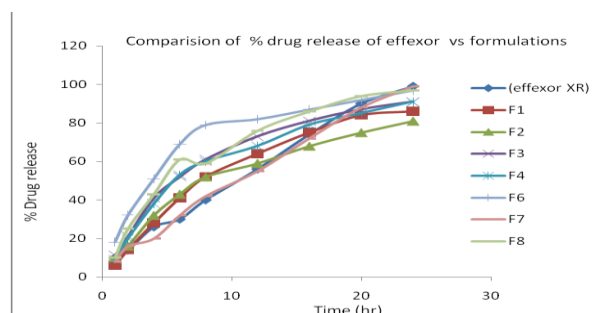
Pre-compression Studies

Bulk density, tapped density, compressibility index and Hausner's ratio test was performed. The prepared blends of various formulations showed bulk density in the range of 0.30 to 0.51, which indicates the flow of blends is fair to good; tapped density in the range of 0.42 to 0.71 g/ml respectively, which indicates that there is a good flow. The % compressibility index range was found to be 24 to 33%, which indicates the flow is poor and passable of the blends and Hausner's ratio in the range of 1.32 to 1.50, Hausner's ratio indicates the flow is poor. (Table 2)

During the granulation of Formulation F1 & F2, localized wetting was observed which resulted in the formation of very hard granules which was then milled by using a Quadra co-mill. A blend of all the formulations was having poor flow as the API was very fluffy.
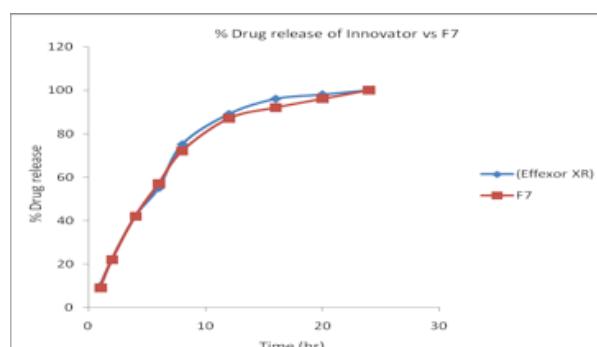
Post Compression Studies

The % weight variation of the formulations are within the limit. The hardness was within the limit and matching the marketed formulation product. The thickness of all the formulations was found to be in the range for core tablets 5.75 to 6.06 mm and for coated tablets 6.09-6.67). Friability limit was according to USP, i.e., 0.5 to 1 %. The values mentioned for all the tests were found to be within the limit (Table 3 and 4). Hardness, thickness,

friability tests were performed for the core and coated tablets and all the results were within limits according to USP.

Figure 1: Comparison of the dissolution profile of venlafaxine HCl formulations Vs marketed formulation

Figure 2: Comparison of dissolution profile of venlafaxine HCl in formulation F7 with marketed formulation
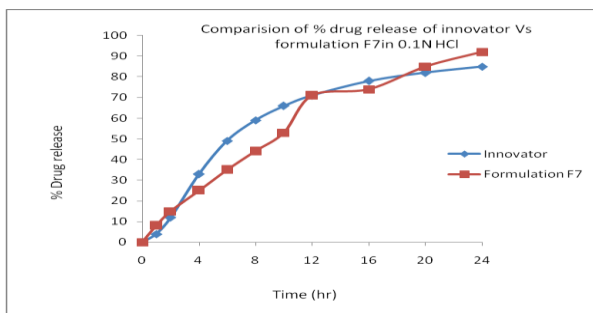
Dissolution Test

In vitro dissolution study was carried out using water as a dissolution media and % drug release of different formulations at various time intervals up to 24 hours was determined. Formulation F7 was found to be matching with marketed formulation product up to 99% of drug release for 24 hours. (Figure 1 & 2)
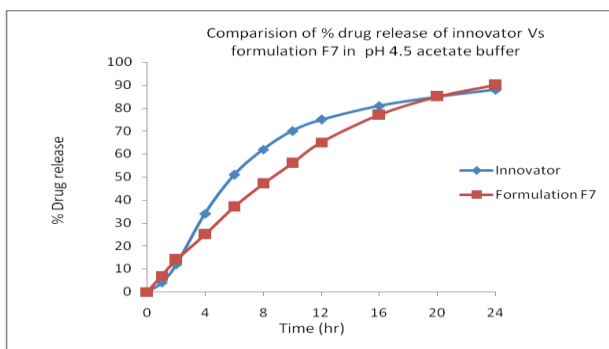
The dissolution analysis was performed for both marketed formulation and F7 formulation in the multimedia dissolution and the data is compiled for marketed formulation and F7 formulation. The % drug release in the multimedia dissolution test was found to be more in the F7 formulation than the marketed formulation product as shown in figures 3, 4 & 5.
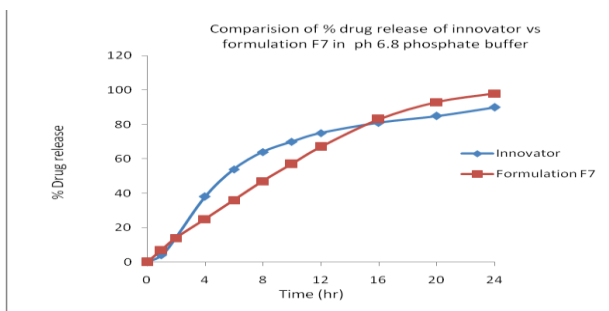
In vitro Release Kinetics

As the drug was water soluble, it was difficult to retard the release by using HPMC alone. Hence the combination of water soluble and water insoluble polymer, i.e., HPMC and Ethylcellulose respectively were used to release the drug as that of marketed formulation. The kinetics of drug release from the extended-release tablets of marketed formulation product and F7 were studied and the linear plot was obtained in various kinetic models (Table 5).

Figure 3: Comparison of % drug release of marketed formulation Vs. F7 in 0.1N HCl

Figure 4: Comparison of % drug release of marketed formulation Vs. F7 in pH 4.5 acetate buffer

Figure 5: Comparison of % drug release of marketed formulation Vs. F7 in pH 6.8 phosphate buffer

Based on the correlation coefficient values for the various kinetic models, the Zero Order kinetics for marketed formulation and F7 was observed. Hence the release of Venlafaxine hydrochloride from the ER is independent in its concentration. The Higuchi model also shows R^2 value for marketed and F7 formulation to be 0.955 and 0.956 respectively; hence the mechanism of drug release is predominantly diffusion. Korsmeyer-Peppas model yields an R^2 value of 0.811 and the 'n' value to be 1.048 (n>1.0) for both the formulations; hence the drug release follows case II transport.

Stability Data of Formulation F7

Dissolution trials of F7 tablets were compared with a marketed product. So, tablets of this batch were kept for stability studies.

The results of stability studies are shown in Table 6. After one month, the physical parameters of the tablets were the same. Water content and related substance were within limits. The tablets were tested for Physical appearance, assay, related substances, dissolution at initial, 1st month, 2nd month and 3rd month in accelerated conditions (40 ± 2°C & 75 ± 5 %RH).

Stability studies for the optimized tablets were carried out at a temperature and relative humidity of 40°C/ 75% ± 5% RH for three months. Tablets were evaluated for physical appearance, colour, assay, loss on drying and results are shown in table 6. Average drug content of the tablets was found to be 99.72% w/w. Tablets have not shown any significant change during storage. Hence, it was concluded that the optimized tablets have good stability during their shelf life.

CONCLUSION

Venlafaxine HCl extended-release tablets were formulated and evaluated to achieve Zero order kinetics by the use of different controlled release polymers. Matrix and reservoir principle was utilized to release the drug as that of marketed product which followed the zero-order release by osmotic principle. To achieve this goal, various formulation trials were taken and evaluated with respect to the various quality control tests. The formula was finalized by comparing the *in vitro* dissolution profile with that of the marketed product. Among all the formulations developed by the wet granulation method, F7 showed highest % drug release (99%) at 24 hours which also followed Zero order kinetics.

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