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Formulation and evaluation of Venlafaxine HCl microspheres

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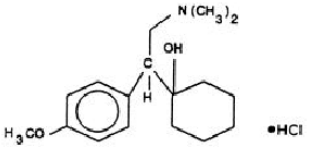
Abstract:

Venlafaxine HCl is the freely water soluble drug with antidepressant activity. It is available in a dose of 25mg-45mg. Being highly soluble drug there is possibility of burst effect which causes sudden peak levels of drug in blood. It is having many side effects and with a half life around 5 hours. To reduce the adverse effects due to burst effect and to have the sustain action of the drug we have prepared the ethyl cellulose microspheres of the drug. The microspheres were prepared by the emulsification and solvent evaporation method. The prepared microspheres were evaluated mainly for the sustain release of the drug and then the anti depressant activity in albino mice apart from the other tests like % drug encapsulation, particle size and drug polymer compatibility by the FTIR studies. The method had resulted in good encapsulation efficiency and micron sized ethyl cellulose spheres. The drug release was found to be sustained for 16 hours and was found to follow the Peppas kinetics.

***Key words*:** Venlafaxine HCl, anti depressant activity, ethyl cellulose microspheres, sustain release dosage forms.

1. **Introduction**

Venlafaxine HCl , commercially known as “Effexor” is a representative of a new class of antidepressants. It is a bicyclic phenylethyl amine and chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents and designated as (R/S)-1-[2-dimethyl amino)-1-(4-methoxy phenyl) ethyl] cyclohexanol hydrochloride. This medication is used to treat anxiety.



venlafaxine hydrochloride

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Venlafaxine HCl is a water soluble drug with a solubility of 572mg/mL[1]. By preparing the sustain release dosage form, the initial burst effect of highly water soluble drugs like Venlafaxine HCl can be prevented.

It acts by inhibiting selectively the uptake of serotonin and nor-adrenaline but shows no affinity for neurotransmitter receptors[2]. It has many adverse effects like nausea, asthenia, dizziness, insomnia, somnolence, headache, dry mouth, sweating, hypotension, nervousness and abnormal ejaculation. The half life of Venlafaxine HCl and its active metabolite O-desmethyl venlafaxine are 5hr and 11hr respectively[3]. A Venlafaxine HCl overdose may be more serious than an overdose with selective serotonin reuptake inhibitors[4].

Antidepressants have characteristics that make the drugs suitable for controlled-release formulations, which might have advantages over immediate-release formulations. For example, controlled-release formulations are associated with lower peak plasma drug concentrations and less fluctuation between peak and trough plasma drug concentrations. In addition to having more stable pharmacokinetic profiles, some controlled-release formulations are associated with lower incidences of nausea than are immediate-release formulations of the same medications. Therefore, some patients who experience intolerable nausea with an immediate-release formulation despite seeing improvement in their depressive symptoms might benefit from taking a controlled-release formulation of the same antidepressant or switching to another of the newer antidepressants. The serious morbidity associated with untreated or inadequately treated depression implies that major benefits may occur in the quality of life for patients who can be salvaged from discontinuing therapy with the use of the most tolerable drug formulations[5].

The main object of our study is to prepare a sustained release dosage form and thus to reduce the complications of Venlafaxine HCl overdose.

2. **Materials and Methods:**

Venlafaxine HCl was a gift sample from Dr. Reddy's, ethyl cellulose, low viscosity grade (250cps in 2% solution at 25ºC) liquid paraffin and span-80 were purchased from SD Fine chemicals (Mumbai), all other chemicals & solvents were of analytical grade.

2.1. **Preparation of the microspheres:**

Two formulae were prepared by taking drug: polymer ratio of 1:1 and 1:2. The microspheres were prepared by this method and named as F1 and F2 respectively. **I**n this method 50 mL of acetone was taken, to this required quantity of ethyl cellulose was added and dissolved. To this drug was added. This dispersed phase was added to continuous phase (100mL) consisting of liquid paraffin containing 0.5% (w/v) span-80 to form water in oil (w/o) emulsion. Stirring was continued at 2000 rpm using a magnetic stirrer for 2 hrs to obtain microspheres.

The microspheres were separated by filtration and washed first with petroleum ether and then with distilled water to remove the adhered liquid paraffin. The microspheres were then finally dried at room temperature.

2.2. **Determination of micromeritic properties.**

The mean particle size of the ethyl cellulose micro spheres was determined by the sieving method[6].

2.2.1. *Entrapment efficiency of the drug*

The micro spheres equivalent to 10mg of Venlafaxine HCl were weighed and dispersed in PBS of pH 7.4. The resulting mixture was agitated on mechanical shaker for 24 hours. The solution was then filtered and drug content was estimated by UV spectrophotometry.

2.3. *FTIR study*

IR spectra of the Venlafaxine HCl, pure ethylcellulose and the drug with ethylcellulose were obtained and were compared for the compatibility.

2.4. *In vitro drug release*

The in vitro release of the drug from microspheres was studied in Phosphate buffer of pH 7.4 (900mL) by using USP basket type dissolution rate test apparatus (ELECTROLAB-TDT 08L) at 100rpm. Microspheres equivalent to 100mg of Venlafaxine HCl were used in each test. Samples were withdrawn at different time intervals and assayed by single beam UV Spectrophotometer (ELICO SL 159) at 229nm.

2.5. *Model fitting for drug release*

The suitability of several equation that are reported in the literature to identify the mechanisms for the release of drug was tested with respect to the release data up to the first 50% drug release. The data were evaluated according to the following equations:

Zero order model [7]

$M_t = M_0 + K_0 t$

Higuchi model[8, 9]

$M_t = M_0 + K_H t^{0.5}$

Korsmeyer-Peppas model[10, 11]

$M_t / M_\alpha = K_K t^n$

Where Mt is the amount of drug dissolved in time t. M_0 is the initial amount of the drug. K_0 is the Zero order release constant, K_H is the Higuchi rate constant, K_K is a Peppas release constant and n is the release exponent that characterizes the mechanism of drug release.

3. **Anti depressant activity:**

Animals:

Albino mice of either sex weighing between 20-25g bred in central animal house of Nalanda College of Pharmacy were used. The animals were housed under standard laboratory conditions and maintained on natural light and dark cycle and had free access to food and water.Animals were acclimatized to laboratory conditions before the experiment. Each animal was used only once. The experiments were conducted according to the CPCSEA guidelines.

Phenobarbitone induced hypnosis:

It is one of the animal models to test the sleep promoting or sedative properties of the drug. Phenobarbitone Sodium (45mg/kg I.P.) was used to induce sleep. The sleep time (onset of sleep) and duration of sleep were recorded after giving the venlafaxine of 10mg/Kg equivalent microspheres (F1) orally[12].

4. **Results and Discussion**

The prepared micro spheres were almost spherical in shape and these are having the average particle sizes of 65.60 ± 0.255 and 126.39 ± 0.502 for the formulations F1 and F2 respectively where n=3. This indicates that the increase in the polymer concentration has increased the average particle size of the micro spheres and this may be due to the reason that the viscosity of the solution was high with increase in the polymer concentration. The micro photograph picture of the Venlafaxine micro sphere was shown in the figure 1. The drug entrapment efficiency was found to be 77.87%± 0.325 and 81.56%±1.254 for F1 and F2 respectively. The entrapment efficiency also got increased with increase with the ethyl cellulose concentration.

IR spectra of the Venlafaxine HCl, polymer and the drug along with polymer have revealed that there is no shifting of the peaks indicating the compatibility of the polymer with the drug Venlafaxine HCl. The FTIR data was given in Figure 4.

The release profile of Venlafaxine HCl from micro spheres exhibited more sustained release with increased polymer concentration and release rate was found in the order of F1‹ F2. This indicates decreased drug release rate is due to increased thickness of the polymer[13]. Statistical data was presented in table no. 1 for F1.

In order to determine the mechanism of drug release from the micro spheres the dissolution data was put in to various models and among them the formulation F1 was best fit in to Korsmeyer-Peppas equation indicating that the drug release is following the non-fickian diffusion. The ‘n’ value for the Korsmeyer- Peppas equation was 0.7550. Details were given in table no.2. In the antidepressant activity evaluation it was found that the sleeping time with F1 was decreased by 45 minutes and the onset of sleep was late by 3 minutes.

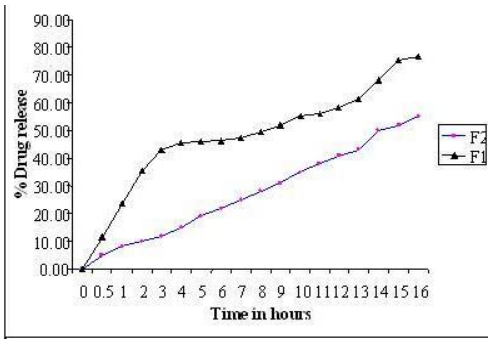


Fig. 2 Comparison of % drug release from formulation F1 and F2 in PBS 7.4

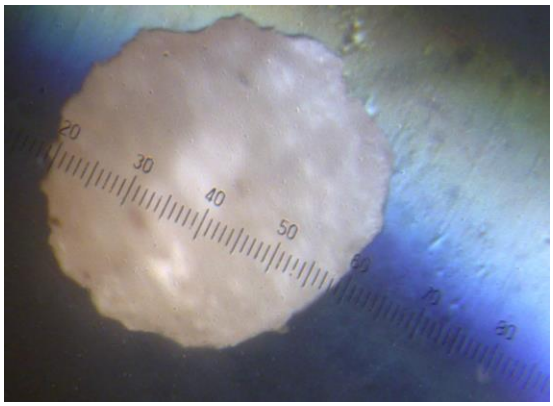


Fig. 1 Microphotograph Venlafaxine ethyl cellulose microsphere.

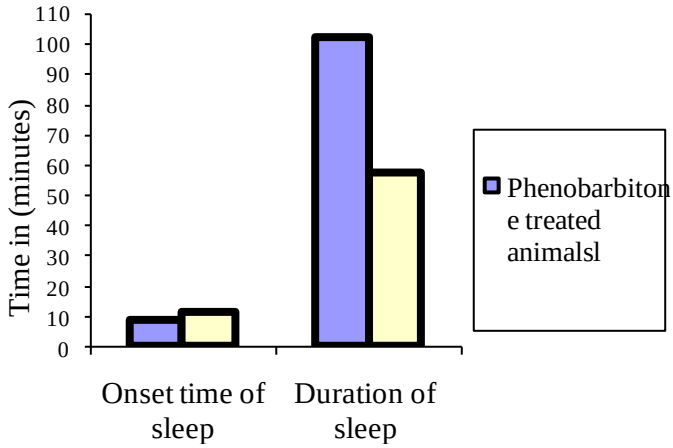


Fig. 3 Onset time and duration of sleep in mice injected with Phenobarbitone (I P) followed by the micro spheres of the drug Vs Distilled water as control.

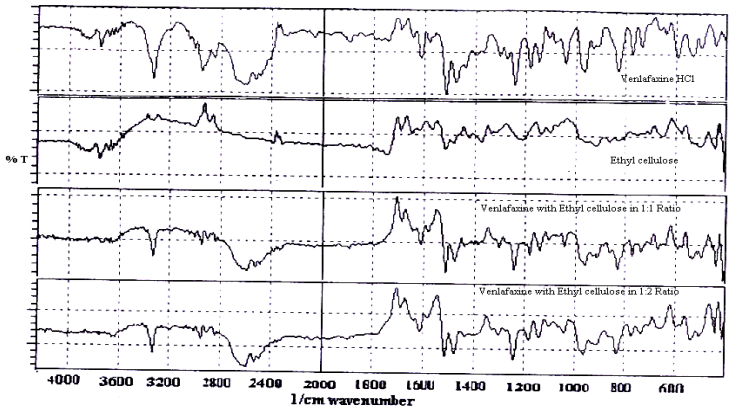
Table 1. Statistical dissolution data for formulation 1

Sr.No.	Time (Hrs)	Avg. %R	SD	SE-mean	RSD
1	0	0.000	0.00	0.00	0.00
2	0.5	11.612	0.27	0.19	2.36
3	1	23.709	0.11	0.08	0.46
4	1.5	35.325	0.65	0.46	1.84
5	2	42.762	0.65	0.46	1.52
6	2.5	45.671	0.16	0.11	0.35
7	3	45.940	0.27	0.19	0.58
8	3.5	46.203	0.16	0.11	0.34
9	4	47.131	0.58	0.41	1.23
10	4.5	49.233	0.37	0.26	0.75
11	5	51.861	0.31	0.22	0.60
12	6	55.334	0.16	0.11	0.28
13	7	55.957	1.19	0.84	2.12
14	8	58.089	0.15	0.11	0.26
15	10	61.346	0.46	0.32	0.75
16	12	68.032	0.61	0.43	0.89
17	14	75.274	0.05	0.04	0.07
18	16	76.657	1.65	1.17	2.15

Table 2. Model fitting data for both the formulations

S.No	*Zero- order Equation*		*Higuchi Equation*		*Korsmeyer-Peppas Equation*			First –order Equation	
	K_0	*R*	K_H	*R*	K_K	*n*	*R*	K_1	R
F1.	7.440	0.8481	23.960	0.9175	22.6414	0.7550	0.9687	-0.0299	-0.9311
F2.	2.1980	0.9118	10.2974	0.8954	10.6074	0.4797	0.7682	-0.1865	-0.9410

Fig 4: FTIR spectra of Venlafaxine HCl with Ethyl cellulose.



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