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Formulation and optimization of orodispersible tablets containing an antidepressant

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ABSTRACT

Venlafaxine hydrochloride is used in the treatment of depression and anxiety disorders. The objective of the present study was to prepare the orodispersible tablets of venlafaxine hydrochloride by sublimation method. Camphor and menthol are used as subliming agents. Tablets are prepared by direct compression process with calcium silicate and sodium starch glycolate as super disintegrants and mannitol as bulking agent. The prepared tablets were evaluated for hardness, friability, in vitro dispersion time, weight uniformity, wetting time and for in vitro drug release. Further the tablets were characterized by Fourier Transform Infra Red Spectroscopy and by Differential Scanning Calorimetry. Sublimation of camphor from tablets resulted in superior tablets as compared with tablets prepared with menthol as sublimating agent. Among all the formulations the tablets prepared by sublimating camphor with sodium starch glycolate as super disintegrant showed faster disintegration and rapid drug release.

Key words: Venlafaxine hydrochloride, Sodium starch glycolate, Calcium Silicate, Sublimation.

INTRODUCTION

The tablet is the most popular dosage form because of its convenience in terms of self-administration and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed novel drug delivery systems known as orodispersible tablets [1-2]. Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients. Difficulty in swallowing conventional tablets and capsules is common among all age groups, especially in elderly and dysphagic patients. This disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy [3-4]. Orodispersible tablets are suitable for formulating drugs undergoing high first pass metabolism and are improving bioavailability with reducing dosing frequency to minimize side effect. The technologies used for preparation of orodispersible tablets include lyophilization, molding, direct compression, cotton candy process; spray drying, sublimation and nanonization [5-6]. These techniques are based on the principles of increasing porosity and/or addition of superdisintegrants and water soluble excipients in the tablets. Superdisintegrants can help to facilitate drug dissolution and subsequently improve bioavailability. In sublimation method, the rapid disintegration of the tablets is achieved by creation of pores in the tablets up on sublimation of volatile components added in the tablets. The saliva will enter these pores and cause the rapid disintegration of the tablets in the oral cavity. The porous structure

is responsible for the faster water uptake, Hence it facilitates wicking action in bringing about faster disintegration[7-8].

Venlafaxine hydrochloride a novel antidepressant having serotonin/nor adrenaline uptake inhibiting effect [9]. It is available as a white crystalline solid and is freely soluble in water and the half life of Venlafaxine HCl is 5 hrs. Based on the above Biopharmaceutical properties it was selected as drug candidate for preparing oral controlled release matrix tablets.

The aim of the present investigation was to prepare optimized orodispersible tablets (ODT) of venlafaxine HCl using various sublimating materials like menthol and camphor and by adding superdisintegrants like sodium starch glycolate and calcium silicate. The prepared tablets were characterized by differential scanning colorimetry (DSC), fourier transform infrared spectroscopy (FTIR) and by *in vitro* dissolution studies.

MATERIALS AND METHODS

Venlafaxine hydrochloride a gift sample from m/s Dr. Reddy Labs, Hyderabad, India. sodium bicarbonate commercially procured from qualigens fine chemicals, Mumbai. Sodium starch glycolate commercially procured from Loba chemie, Mumbai. calcium silicate a gift sample from pellets pharma, Hyderabad. Mannitol, Talc, Magnesium stearate are procured by Laba chemie, cochine. Other materials used re of analytical grade.

Preparation of ODT by sublimation Method

Orodispersible tablets containing venlafaxine were prepared by direct compression process. The drug mannitol, various sublimating materials like menthol, camphor and superdisintegrants like sodium starch glycolate and calcium silicate and magnesium stearate were passed through sieve no. 60 mixed and blended followed by compression of the blend on a 10 station rotary compression machine using 10 mm round flat punches. After compression the tablets were collected and vacuum dried at 60°C until a constant weight was obtained to ensure the complete removal of sublimable components to make the tablet porous.

Characterization of ODT

FTIR Spectral Analysis

Infrared spectra of drug and excipients were recorded by KBr pellet method using Fourier Transform Infrared Spectrophotometer (BRUKER 8400S). A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded. The samples were prepared by KBr pellet press method. The spectra are shown in the figures 3-5.

Differential scanning Colorimetry (DSC)

The DSC studies were performed for pure drug, and for selected formulations. These studies were carried out with PERKIN ELMER DSC model 7 using Al 40 µl crucible at 10^0 C/min heating range. The temperature range used was 0 – 300^0C. the thermograms were shown in the figures 6-8.

Evaluation of fast Dissolving tablets

Physical parameters such as weight variation, hardness, friability and disintegration were evaluated for prepared tablets. The prepared orodispersible tablets were further evaluated for physical parameters like drug content, wetting time, water absorption ratio, moisture uptake studies and for *in vitro* dissolution studies.

The moisture uptake study was carried out by keeping ten tablets along with calcium chloride in a desiccator maintained at 37 °C for 24 h to ensure complete drying of the tablets. The tablets were then weighed and exposed to 75% RH, at room temperature for 2 weeks. The required humidity can be achieved by keeping saturated sodium chloride solution in the desiccator for 24 h. The tablets are reweighed and the percentage increase in weight was recorded. If the moisture uptake tendency of a product is high, it requires special dehumidified area for manufacturing and packing of the tablets [10].

Wetting time is carried out by taking five circular tissue papers of 10 cm diameter were placed in a Petri dish with 10 cm diameter. 10 ml of water containing Amaranth, water soluble dye was added to the petri dish. One tablet was carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as a wetting time [11].

Disintegration time of orodispersible tablets were carried out by the method given by Gohel. [12] for this a Petri dish was filled with 10 ml of water and the tablet was carefully placed in the centre of petri dish and the time taken for the tablet to completely disintegrate in to fine particles was noted.

***In-vitro* dissolution study:**

The dissolution test was carried out in USP apparatus type II (Paddle) with 900ml of distilled water as the dissolution medium. The samples were drawn at 5, 10,15,30,45 minutes. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by ELICO double beam spectrophotometer at 225nm and subsequently analyzed for the cumulative percentage of drug released. The dissolution studies on each formulation were conducted in triplicate.

The dissolution profiles of all the ODT formulations for venlafaxine hydrochloride were compared with the marketed immediate release formulation by using a model independent approach of similarity factor, *f2*, with all time points included in the *in vitro* dissolution studies [13]. Similarity factor, *f2* is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves of marketed and test formulations. The equation for calculating similarity factor is

$$f_2 = 50 \times \log \{ [1+(1/n) \sum_{J=1}^{N} | R_t - T_t |^2]^{-0.5} \times 100 \}$$

Where 'n' is the number of dissolution time and R_t and T_t are the reference (theoretical) and test dissolution values at time 't'. Dissolution profile was considered satisfactory if *f*2 value is more than 50. Two dissolution profiles are considered similar when the f2 value is 50 to 100.

RESULTS

Orodispersible tablets of venlafaxine were prepared by using superdisintegrants SSG and CS in different concentrations i.e., 20 and 25%. . The compositions of various tablet formulations are given in table 1. The flow properties such as angle of repose and Carr's index were evaluated for various tablet powder formulations and were found to exhibit good flow characteristics. The angle of repose values obtained for various formulations were in the range of 20.18±0.5 - 25.62±0.2 and Carr's index were in the range of 11.24±0.6 -19.27±0.5 %. Hausner's ratio for various formulations were in the range of 1.11-1.25. Tablet formulations were further evaluated for physical parameters. Moisture uptake studies for orodispersible tablets were conducted to assess the stability of formulation. The hardness of all the tablet formulations were in the range of 3.0 to 3.5 kg/cm2. Weight uniformity of all the tablet formulations were in the range of 200 ± 3 mg/tablet. Friability losses of all the tablet formulations were negligible and were in the range of 0.1 to 0.2%. Drug content estimated for all the tablet formulations was highly uniform with less than 2.5% variation. The results of physical parameters evaluation are given in table 2.

The dissolution studies of orodispersible tablets were performed in distilled water by using USP-II apparatus (paddle method). Based on the data obtained from the dissolution studies, various parameters such as T_{50}, DE_{30}%, first order and zero order release rate constants were estimated. The dissolution parameter such as T_{50} was measured directly from the dissolution profile curves and DE_{30} % was estimated by employing trapezoidal rule to the dissolution profiles. The dissolution profiles of venlafaxine orodispersible tablets were shown in figure 1 and 2. The in vitro dissolution and kinetic parameters were given in table 3.

The possible interaction between the drug and the carrier was studied by FTIR spectroscopy. IR spectra of pure venlafaxine showed characteristic peaks at O-H stretch 3768cm-1, N-H stretching 3323cm-1, C-H stretching in aromatic ring is 3014cm-1, C-H stretching alkane is 2933cm-1. FTIR spectra of the optimized formulations displayed all the characteristic bands of drug, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations. The FTIR spectra were given in figure 3 (Pure Venlafaxine HCl), Figure 4 (Formulation F2) and figure 5 (Formulation F6) .

DSC analysis was performed for the pure drug and for formulations F2 and F6. DSC thermogram for pure venlafaxine shows onset of peak at 214.2 ^{0} c, where as DSC thermograms of optimized formulations F4 and F8 showed onset of peaks at 191.9^0 C and 201.3^0 C indicated that there was no drug and polymer interaction. The thermograms were shown in figure 6 (Pure Venlafaxine HCl), 7 (Formulation F2) and 8 (Formulation F 6).

The dissolution profiles of venlafaxine hydrochloride ODT formulations were compared with marketed immediate release formulation of venlafaxine hydrochloride (Effexor). The similarity factor was calculated for these tablet formulations. The similarity factor f_2 values were in the range of 39 – 79. The formulations F3, F4 and F7 showed the similarity factor values above 50 indicated that the release profiles for these formulations were similar to that of marketed formulation.

Table 1: Compositions of Venlafaxine Hydrochloride Orodispersible Tablets

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Venlafaxine hydrochloride	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
camphor	40	40	--	--	40	40	--	--
menthol	--	--	40	40	--	--	40	40
calcium silicate	40	50	40	50	--	--	--	--
sodiumstarch glycolate	--	--	--	--	40	50	40	50
Mannitol	50	40	50	40	50	40	50	40
Directly compressable lactose (DCL)	30.5	30.5	30.5	30.5	30.5	30.5	30.5	30.5
Magnesium sterate	2	2	2	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200	200	200	200

Table 2: Physical Parameters of Venlafaxine HCl Orodispersible Tablets

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (%)loss	Wetting time (sec)	Disintegration time (sec)	Drug content
F1	198±0.3	3.4	0.16	40	51	36.79
F2	201±0.3	3.5	0.19	28	40	36.95
F3	198±0.3	3.5	0.17	83	92	36.84
F4	201±0.2	3.0	0.15	72	86	36.75
F5	198±0.2	3.1	0.20	38	41	36.93
F6	198±0.3	3.5	0.17	17	30	37.15
F7	200±0.3	3.2	0.19	40	51	36.94
F8	201±0.2	3.0	0.17	42	49	37.08

Table 3: *In Vitro* Dissolution Parameters of Venlafaxine Hydrochloride Orodispersible Tablets

Formulation	Similarity Factor (f2)	T_{50} %	DE_{30}%	Zero Order Constant		First Order Constant	
				K(min^{-1})	R^2	K(min^{-1})	R^2
F1	40	9±0.2	80.0±0.4	1.1445	0.778	0.017	0.925
F2	32	8±0.4	81.2±0.5	1.1227	0.757	0.019	0.931
F3	79	8± 0.4	74.3±0.2	1.1101	0.739	0.021	0.932
F4	72	6± 0.4	78.5±0.5	1.1192	0.717	0.026	0.952
F5	41	6±0.5	80.7±03	1.1380	0.779	0.018	0.931
F6	39	4±0.3	86.2±0.4	1.1706	0.772	0.021	0.949
F7	60	8±0.2	78.0±0.4	1.1469	0.755	0.023	0.948
F8	44	6±0.5	80.4±0.2	1.0975	0.722	0.027	0.957

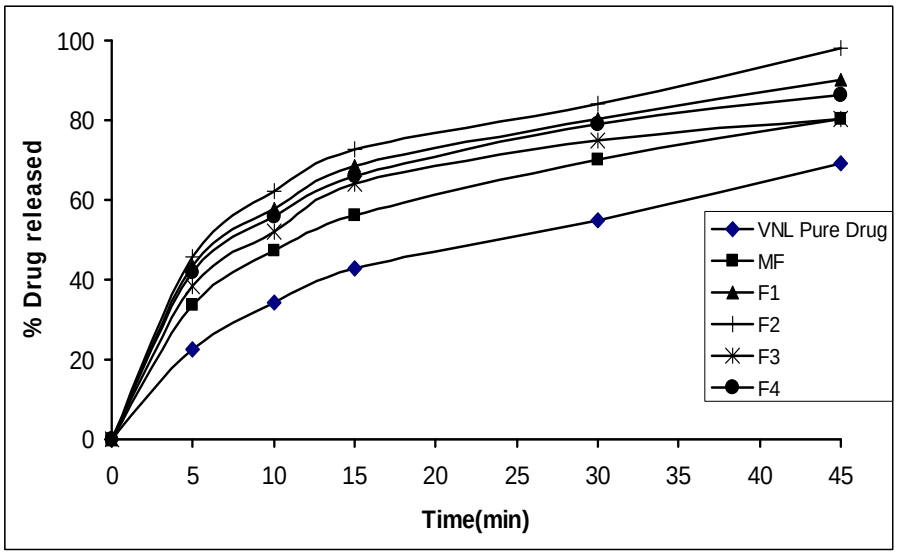

Figure 1: Dissolution Profiles of Venlafaxine Orodispersible Tablets
(MF = Marketed Formulation)

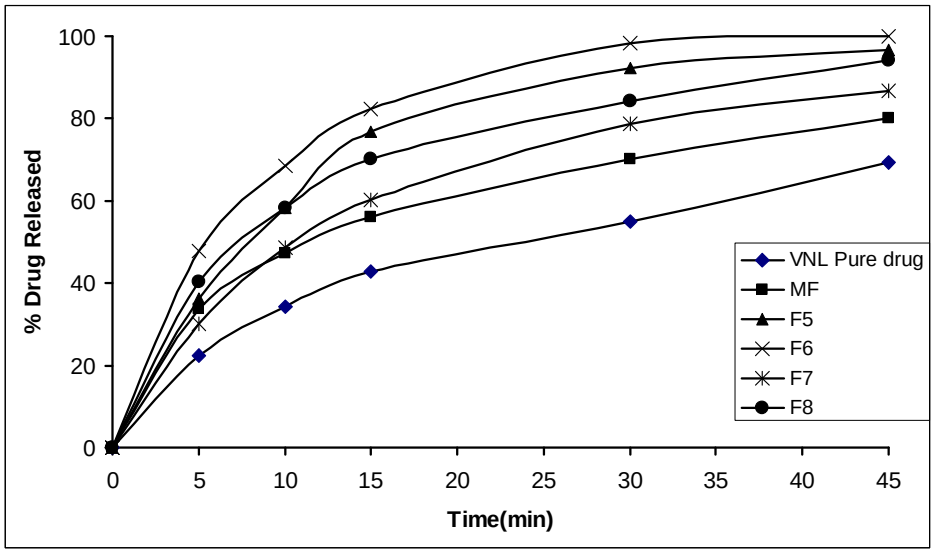

Figure 2: Dissolution Profiles of Venlafaxine Orodispersible Tablets
(MF = Marketed Formulation)

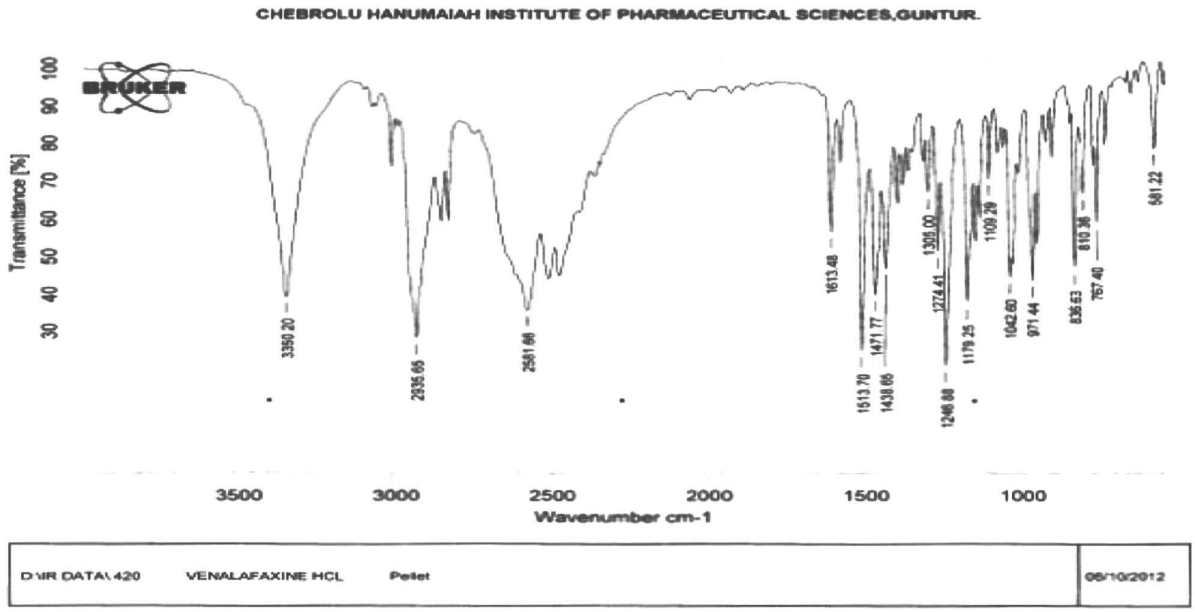

Figure 3: FTIR Spectra of Venlafaxine HCl API

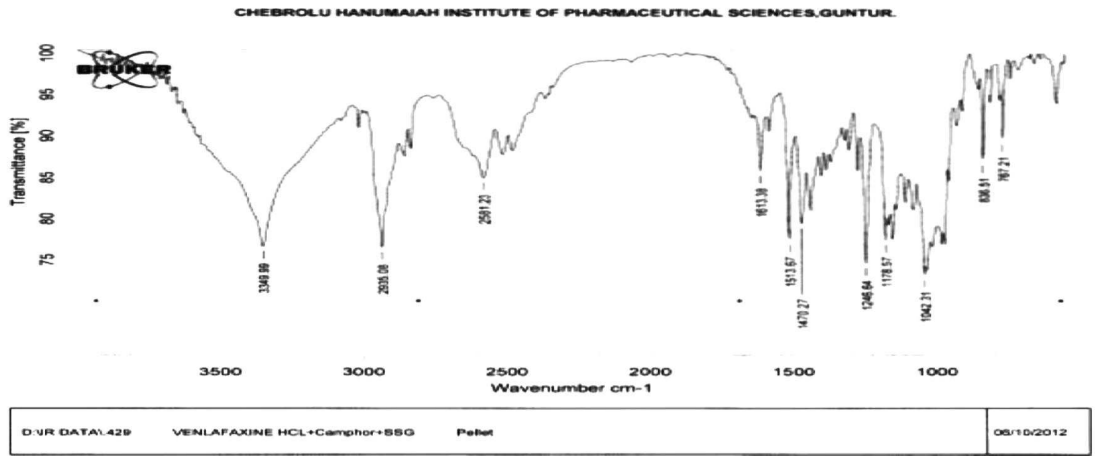

Figure4: FTIR Spectra of Formulation F2

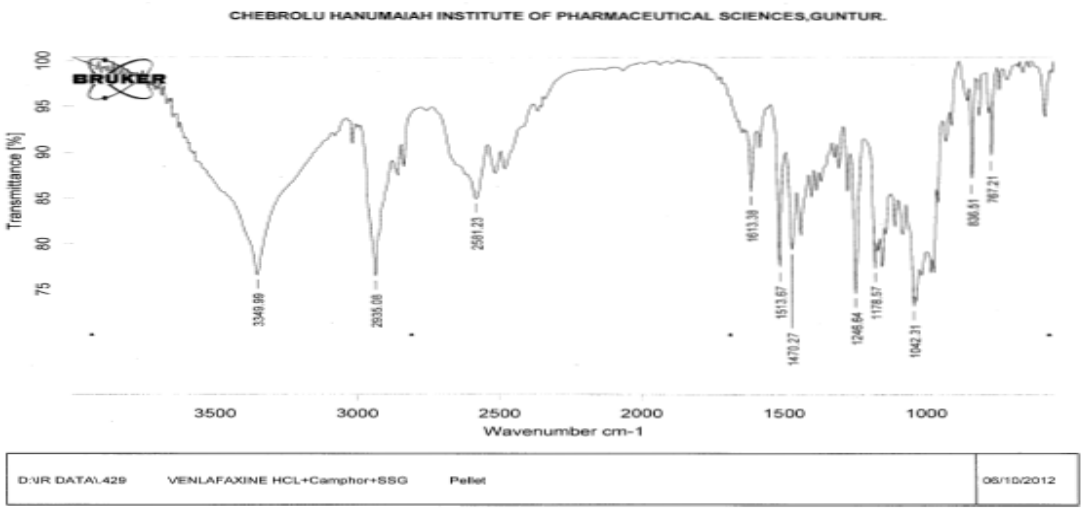

Figure 5: FTIR Spectra of Formulation F6

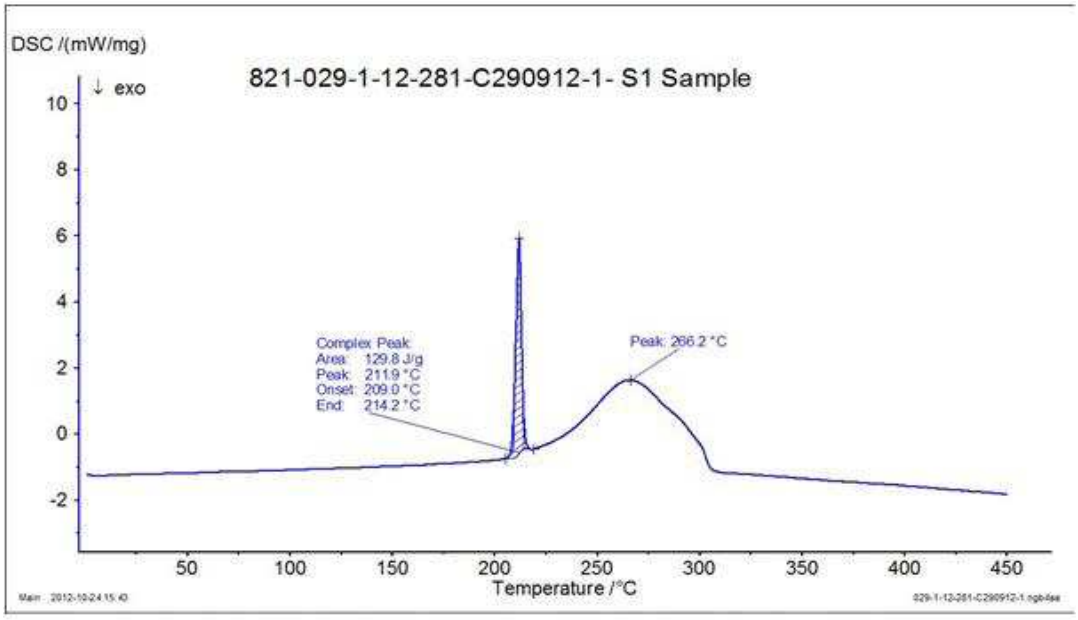

Figure 6: DSC Thermogram of Venlafaxine HCl API

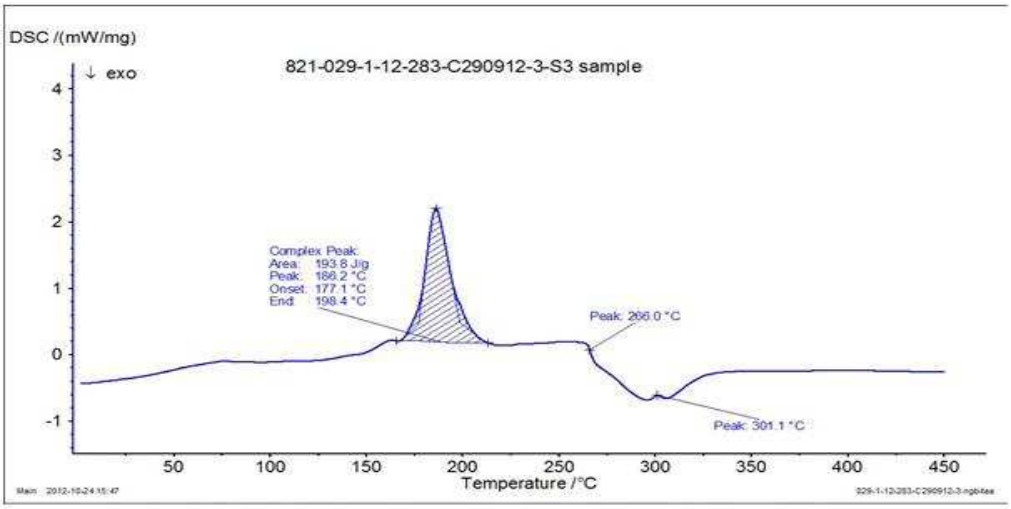

Figure 7: DSC Thermogram of Formulation F2

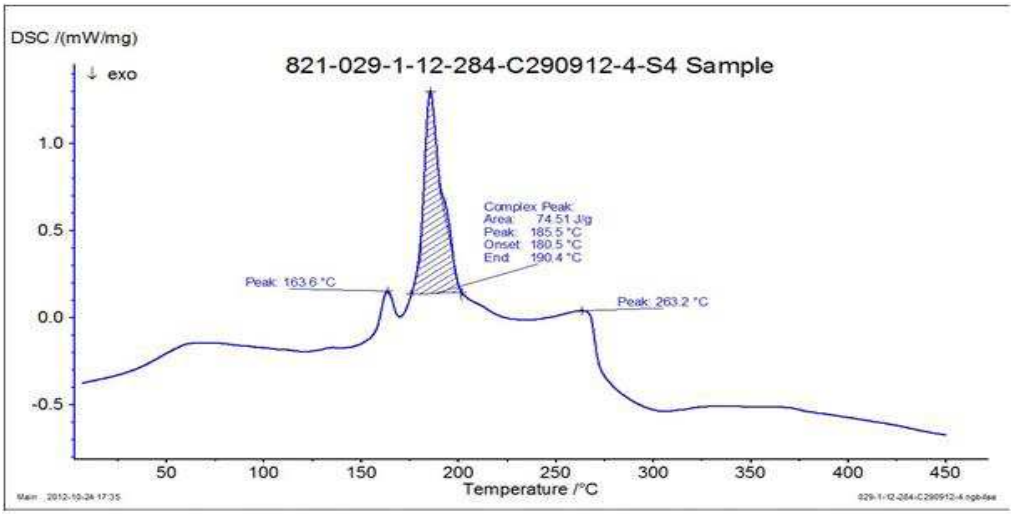

Figure 8: DSC Thermogram of Formulation F6

DISCUSSION

Orodispersible tablets of venlafaxine were prepared by using superdisintegrants SSG and CS. The powder formulations evaluated for flow properties such as angle of repose and Carr's index were evaluated for various tablet powder formulations and were found to exhibit good flow characteristics. Tablet formulations were further evaluated for physical parameters and for moisture uptake studies to assess the stability of formulation. The results revealed that all the batches of tablet formulations were found to be stable and suitable for further investigations. The dissolution studies of orodispersible tablets were performed in distilled water by using USP-II apparatus (paddle method). The drug release rate from all the tablet formulations was found faster as compared to pure drug. Addition of camphor in the formulation improved the tablet properties with respect to wetting time and in vitro dispersion time. Comparatively increased concentration of camphor in formulation F2 and F6 showed relatively decreased wetting time which may be attributed to faster uptake of water due to the porous structure formed thus facilitating the disintergrant to bring about faster disintegration. The rapid drug dissolution might be due to easy breakdown of particles due to porous structure formation after sublimation of camphor and rapid absorption of drugs into the dissolution medium when compared with porous structure formation by sublimation of menthol. The possible interaction between the drug and the carrier was studied by FTIR spectroscopy and by DSC analysis. The results suggested that there was no potential chemical interaction between the components of the formulations.

CONCLUSION

From the present study, it is concluded that the tablets of venlafaxine HCL prepared by sublimation technique using menthol and camphor sublimating agent are suitable for orodispersible. Sublimation technique would be an alternative approach to use of more expensive adjuvant and sophisticated instruments in the formulation of orodispersible tablets. The prepared tablet gives benefit in terms of patient compliance, rapid onset of action, increased bio-availability, low side effect and good stability which make these tablets popular as a dosage form for the treatment of depression and anxiety disorders.

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