Research Article

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Formulation and evaluation of venlafaxine hydrochloride mouth dissolving tablets by effervescent technique

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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 mouth dissolving tablets of venlafaxine hydrochloride by effervescent method. sodium bicarbonate, citric acid and tartaric acid were used as effervescent agents. Tablets are prepared by direct compression process with crosscaremellose sodium 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. Among all the formulations the tablets prepared by with sodium starch glycolate as super disintegrant and tartaric acid and sodium bicarbonate as effervescent agents showed faster disintegration and rapid drug release.

Key words: Venlafaxine hydrochloride. Sodium starch glycolate. Croscarmellose sodium, Effervescent agents.

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 mouth dissolving tablets (MDT) [1-4]. 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 [5-6]. The technologies used for preparation of mouth dissolving tablets include lyophilization, molding, direct compression, cotton candy process; spray drying, sublimation and nanonization [7-8]. Superdisintegrants can help to facilitate drug dissolution and subsequently improve bioavailability. Addition of effervescent system in the formulation is one of the approach by which mouth dissolving tablets can be prepared. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide the bitter taste of drug is also masked and a pleasant mouth feel is felt. Citric acid is very hygroscopic and it poses challenge to formulators hence, it was selected where as tartaric acid is comparatively less hygroscopic so it was used in the present work [9-12]. The effervescent agents when incorporated into MDTs, tablets will disintegrate quickly due to the effervescent carbon dioxide. Therefore, the effervescent couples can be regarded as a disintegrant in the MDT formulation. The carbon dioxide generated in the tablet can also improve the overall taste.

Venlafaxine hydrochloride a novel antidepressant having serotonin/nor adrenaline uptake inhibiting effect [13-14] 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 mouth dissolving tablets (MDT) of venlafaxine HCl using effervescent agents like sodium bicarbonate, citric acid and tartaric acid and by adding superdisintegrants like sodium starch glycolate and croscarmellose sodium. The prepared tablets were characterized by differential scanning colorimetry (DSC), fourier transform infrared spectroscopy (FTIR) and by *in vitro* dissolution studies.

MATERIAL AND METHOD

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. Crosscarmellose sodium a gift sample from pellets pharma, Hyderabad. Mannitol, Talc, Mag-

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nesium stearate are procured by Laba chemie, cochine. Other materials used re of analytical grade.

Preparation of MDT by Effervescent Method

Mouth dissolving tablets containing venlafaxine were prepared by direct compression process. In the effervescent method, sodium bicarbonate, citric acid and tartaric acid were pre-heated at a temperature of 60º to remove absorbed/residual moisture. The drug mannitol, various effervescent agents like sodium bicarbonate, citric acid, tartaric acid and superdisintegrants like sodium starch glycolate and croscarmellose sodium 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.

Characterization of MDT

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.

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^{0}C.

Evaluation of Mouth Dissolving tablets

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

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 [15].

Disintegration time of mouth dissolving tablets was carried out by the method given by Gohel et al [16]. 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.

RESULT AND DISCUSSION

Mouth dissolving tablets of venlafaxine were prepared by using superdisintegrants SSG and CP 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 was in the range of 1.11-1.25. Tablet formulations were further evaluated for physical parameters. Moisture uptake studies for mouth dissolving tablets were conducted to assess the stability of formulation. The hardness of all the tablet formulations was 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

Table 1: Compositions of Venlafaxine Hydrochloride Mouth dissolving 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
Sodium bi carbonate	15	15	15	15	15	15	15	15
Citric acid	15	20	—	—	15	20	—	—
Tartaric acid	—	—	15	20	—	—	15	20
croscarmellose sodium	30	40	30	40	—	—	—	—
Sodiumstarch glycolate	—	—	—	—	30	40	30	40
Mannitol	60	60	60	60	60	60	60	60
Lactose	40.5	25.5	40.5	25.5	40.5	25.5	40.5	25.5
Talc	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200

Table 2: Physical Parameters of Venlafaxine HCl Mouth dissolving Tablets

Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (%)loss	Wetting time (sec)	Disintegration time (sec)	Drug content
F1	199±0.3	3.9	0.16	40	51	36.79
F2	201±0.3	3.5	0.19	28	38	36.95
F3	199±0.3	3.5	0.17	73	62	36.84
F4	201±0.2	3.0	0.15	28	32	36.75
F5	199±0.2	3.0	0.20	58	41	36.93
F6	199±0.3	3.5	0.17	17	34	37.15
F7	200±0.3	3.5	0.19	40	38	36.94
F8	201±0.2	3.0	0.17	20	22	37.08

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

Formulation	T_{50}%	DE_{30}%	Zero Order Constant		First Order Constant	
			K(min^{-1})	R^2	K(min^{-1})	R^2
F1	10±0.2	80.0±0.4	1.121	0.628	0.020	0.985
F2	8±0.4	81.2±0.5	1.125	0.657	0.017	0.981
F3	7± 0.4	74.3±0.2	1.124	0.745	0.022	0.982
F4	5± 0.4	78.5±0.5	1.117	0.720	0.019	0.982
F5	8±0.5	80.7±03	1.122	0.679	0.021	0.981
F6	7±0.3	86.2±0.4	1.167	0.801	0.017	0.989
F7	5±0.2	78.0±0.4	1.128	0.685	0.021	0.978
F8	4±0.5	80.4±0.2	1.024	0.702	0.027	0.997

all the tablet formulations was highly uniform with less than 2.5% variation. Thus all the batches of tablet formulations were found to be stable and suitable for further investigations. The results of physical parameters evaluation are given in table 2.

The dissolution studies of mouth dissolving 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. The drug release was rapid from the formulations F4 and F8 containing 10% of tartaric acid and 20 % of super disintegrants. The drug release was rapid from the formulation F8 containing sodium starch glycolate as superdisintegrant when compared with the formulations containing croscarmellose as super disintegrant. The dissolution profiles of venlafaxine mouth dissolving tablets were shown in figure 1 and 2. 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 *in vitro* dissolution and kinetic parameters were given in table 3.

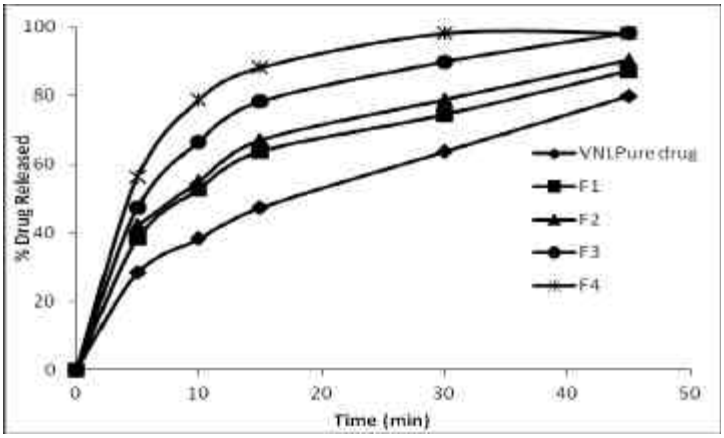

Figure 1: Dissolution Profiles of Venlafaxine Mouth dissolving Tablets

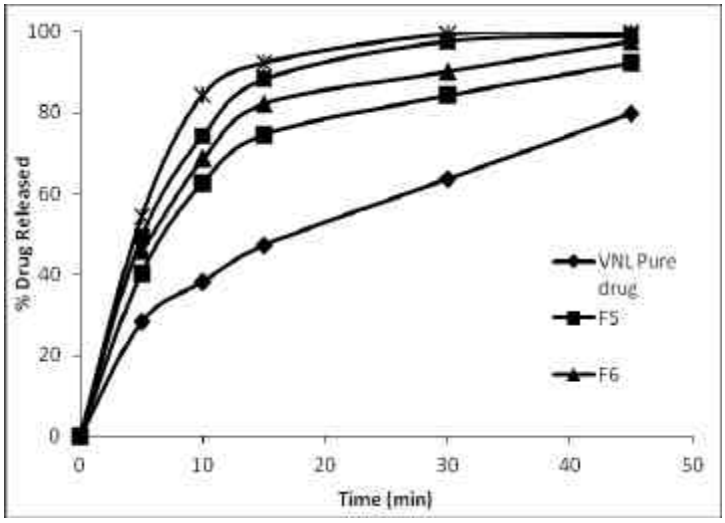

Figure 2: Dissolution Profiles of Venlafaxine Mouth dissolving Tablets

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 3-5.

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

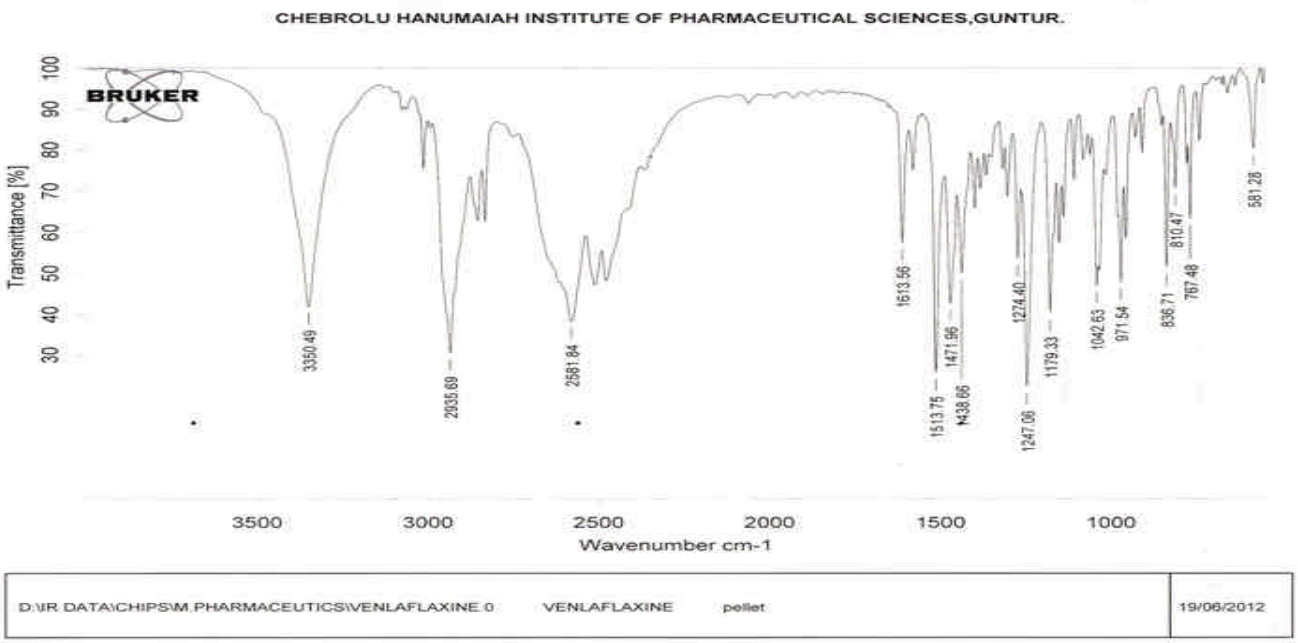

Figure 3: FTIR spectra of Formulation Venlafaxine HCl

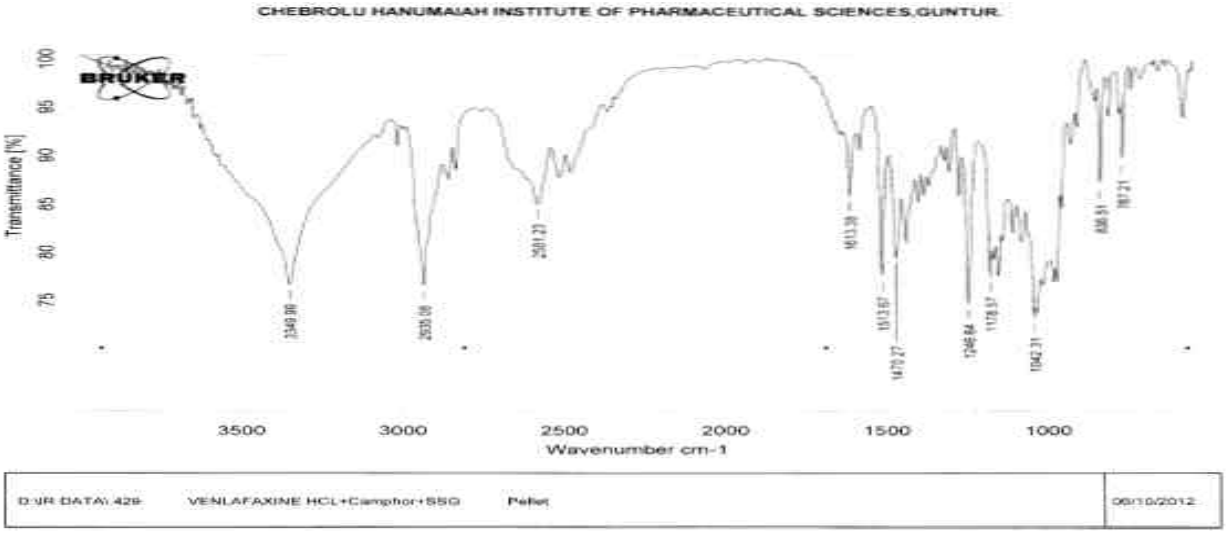

Figure 4: FTIR spectra of Formulation F4

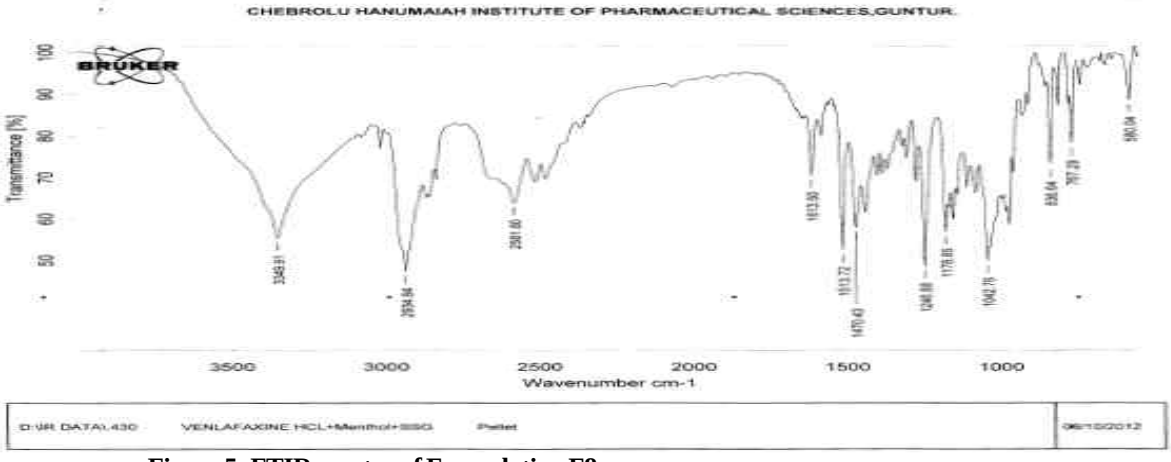

Figure 5: FTIR spectra of Formulation F8

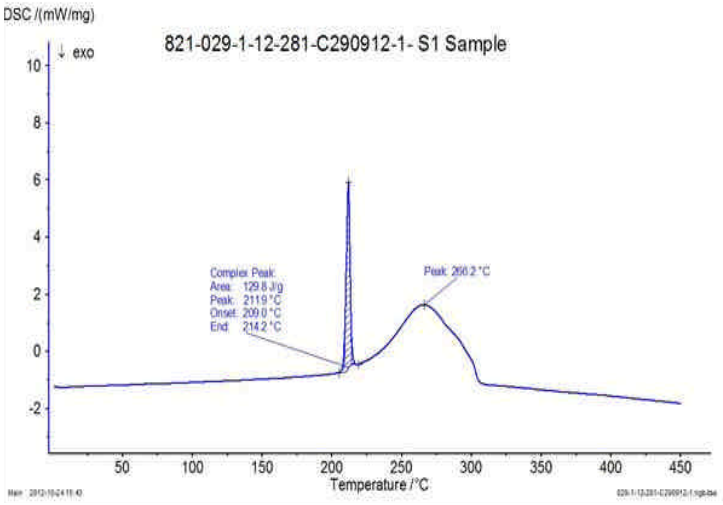

Figure 6: DSC thermogram of Venlafaxine HCl

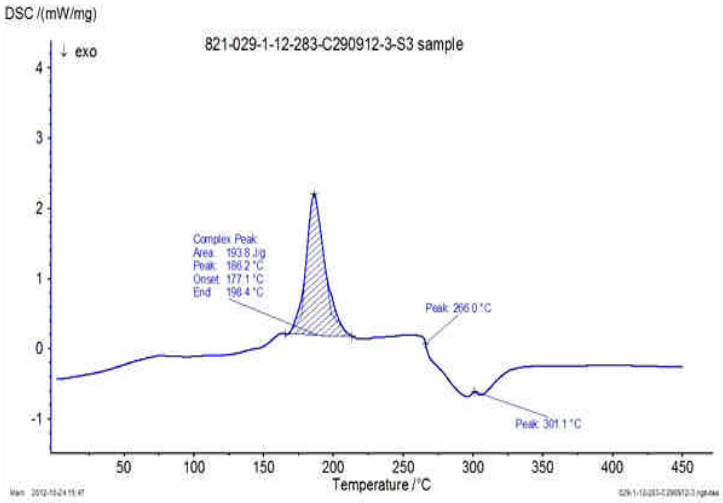

Figure 7: DSC Thermogram of Formulation F4

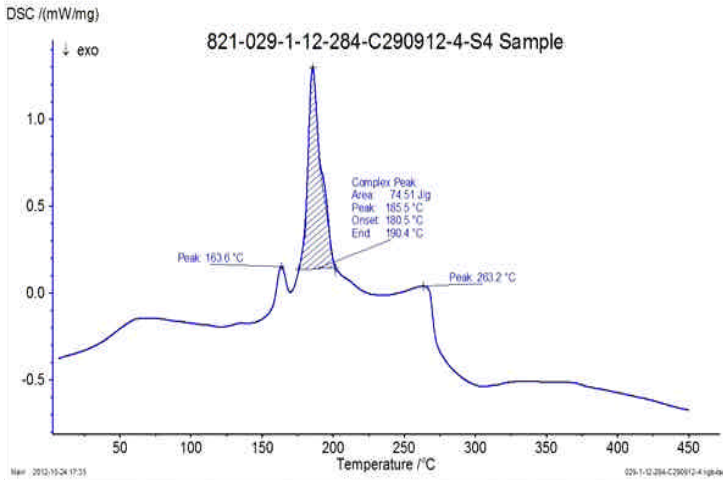

Figure 8: DSC Thermogram of Formulation F8

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 figures 6-8.

CONCLUSION:

From the present study, it is concluded that the tablets of venlafaxine HCL prepared by effervescent technique using citric acid, tartaric acid and sodium bicarbonate as effervescent agents are suitable for mouth dissolving formulations. Effervescent technique would be an alternative approach to use of more expensive adjuvant and sophisticated instruments in the formulation of mouth dissolving 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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