Research Article

Design and Development of a Gastro Retentive Tablet of Venlafaxine Hydrochloride by Wet Granulation Method.

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Abstract

The present investigation describes the design and development of Gastro retentive system of Venlafaxine Hydrochloride. Floating tablets containing Venlafaxine Hydrochloride were prepared by wet granulation technique using varying concentrations of polymers with sodiumbicarbonate.It was found that gastro retention time of Venlafaxine Hydrochloride can be increased by formulating it in a floating dosage form using optimum amount of HPMC, sodium bicarbonate and citric acid. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, invitro buoyancy and dissolution studies. The produced floating tablets exhibited good floating time and controlled drug release over a period of 8 hrs. It was concluded that floating tablet with good flow property and controlled release property can be obtained by optimizing amount of HPMC, sodium bicarbonate and citric acid. Among these formulations of Venlafaxine HCL,F2 showed maximum release and proved to be best.

Keywords: Venlafaxine Hydrochloride, HPMC, Wet granulation, Floating tablets

INTRODUCTION

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical industry to investigate various strategies in the development of new drug delivery systems [1]. Drug release from the delivery devices can be sustained up to 24h for many drugs using current release technologies. However, the real issue in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released [2]. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose [3].

Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Usually, it consists of two compartments. One is responsible for controlling drug release. Hydrogel polymers, such as HPMC or alginates are best for this purpose. Another compartment is for buoyancy to extent gastric retention; low density additives (eg.fatty acid and fatty alcohol) and gas –generating agents (such as bicarbonate) are suitable for this purpose. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine.[11,12]

Several approaches are currently used to retain the dosage form in stomach. These include bio adhesive systems [4] swelling and expanding systems [5, 6], floating systems [7, 8], and other delayed gastric emptying devise [9, 10]. The principle of buoyant preparation offers a simple and practical approach to achieve increased residence time for the dosage form in stomach and sustained drug release.

From the technological point of view, floating drug delivery system is a more convenient and logical approach to prolong gastric residence time.[13,14,15,16].

Materials & Methods

Venlafaxine Hydrochloride obtained from Ranbaxy Lab.Ltd; Gurgaum.HPMC obtained from Colorcon Asia private ltd; Goa.Sodiumbicarbonate, citricacid, lactose, PVPK30, talc, magnesium stearate, isopropyl alcohol etc were obtained from SD Fine chemicals, Mumbai.

Methodology

Preformulation study

The preformulation studies were performed for

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drug as well as polymers. These studies are preliminary identification test, bulk density, tapped density and compressibility index.

Identification test:

Drug:

The solution containing 100microgram/ml of Venlafaxine Hydrochloride in 0.1 N HCl was prepared and scanned over the wavelength range of 220nm to 400nm against water as a blank using double beam UV spectrophotometer. The plot of absorbance against wavelength was recorded using double beam UV spectrophotometer.

Infrared spectrometry is one of the most useful analytical techniques which offer the possibility of chemical identification. For the study of the drug the sample was powdered and intimately mixed with dry powdered potassium bromide with the help of pestle and mortar. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in a FTIR spectrophotometer.[17]

For the study of the polymer, the sample was powdered and intimately mixed with dry powdered potassium bromide with the help of pestle and mortar. The powdered mixture was taken in a diffuse reflectance sampler and the spectra recorded by scanning in a FTIR spectrophotometer.[17] .The IR spectrum of drug was then compared that of the spectrum of the physical mixture to check for any possible drug excipients interaction study.

Venlafaxine HCL has been quantitatively analyzed by various techniques. In the present study, Venlafaxine HCL was estimated by UV spectrophotometric method.

Preparation of standard curve in 0.1N HCL
Venlafaxine HCL(100 mg) was accurately weighed and dissolved in 1000ml of 0.1N HCL to generate a stock solution having concentration of 100μ /ml.1ml of stock solution was further diluted to 100ml to produce standard solution having concentration of 10μ/ml.5 ml of this concentration was further diluted to make standard solution of 5μ/ml.Similarly the standard solution was further diluted with 0.1N HCL to get working standard solution having concentration of 5,10,15,20,25 and 30μ/ml.The absor-

bance of the solutions was measured at 224.6nm using double beam UV visible spectrophotometer against 0.1N HCL as a blank. The plot of absorbance against concentration was plotted and data was subjected to linear regression analysis.

The standard calibration curve of drug in 0.1N HCL was given in fig1.The data of absorbance was shown in table1.The data has correlation coefficient of 0.9951.

Formulation of floating tablets
Floating tablets containing Venlafaxine HCL were prepared by wet granulation technique using varying concentrations of HPMC with sodiumbicarbonate.Weighed accurately all the ingredients including drug, HPMC, sodium bicarbonate, citric acid, lactose and mixed thoroughly with the help of motar and pestle. The quantities of all the above ingredients were taken as per table 2.All the mixed ingredients were passed through sieve no.50.Then granulating solution of PVP K 30 in isopropyl alcohol was prepared and used to make wet mass of above sieved materials. The above wet mass was sieved again through sieve no.12 and dried in hot air oven at a temperature of 41-45C.After drying, the sample granules were again sieved through sieve no.80 and lubricated with magnesium stearate and talc just 4-5 min before compression.

Evaluation
1. Characterization of Granules
Flow property of the granules was evaluated by determining the angle of repose. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The angle of repose was calculated using the equation.
$Tan\theta = h/r$ where h is the height of pile and r is the radius of the pile

Granules were poured gently through a glass funnel into 50ml graduated cylinder. Bulk density was calculated.
Bulk density=M/V_o where M is the mass of powder and V_o is the bulk volume

Granules were poured gently through a glass funnel into 50ml graduated cylinder. Tapped density was calculated.
Tapped density=M/V_t where M is the mass of powder and V_t is the Tapped volume

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Carrs index was calculated according to the following equation

Carrs index= P_t-P_b/P_t x 100 where P_t=tapped density and P_b=bulk density

Tapped density and bulk density were determined and the Hausner ratio was calculated by using the equation

Hausner ratio=P_t/P_b where P_b=bulk density and P_t=tapped density

Characterization of tablets

Tablet density is an important factor for floating tablets. Density was determined by Density=mass/volume

The hardness was measured by taking 10 tablets from each formulation using Monsanto Hardness tester.

Uniformity of weight

20 tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

The friability of 6 tablets was measured using Roche Friabilator. %friability= (loss in weight/initial weight) x100

Drug Content estimation: 20 tablets were weighed and average weight was calculated. The drug content in each formulation was determined.

Study of Floating Properties:

The time between introduction of dosage form and its buoyancy on the surface of medium and the time during which the dosage form remained buoyant were measured. The tablets were placed in a 100ml beaker containing 0.1N HCL.The Time required for the tablet to raise to the surface and float was determined. The duration of time the dosage form constantly remained on the surface of medium was determined. [18]

Dissolution Study:

Dissolution of the tablet of each batch was carried out using USPXXIII type II apparatus using paddle.900ml of 0.1N HCl (pH1.2) was filled in a dissolution vessel and the temperature of the medium were set at 37+-0.5c.One tablet was placed in each dissolution vessel and the paddle rotational speed was set at 50rpm.5ml of sample was withdrawn at every hours for 10hours and same volume of fresh medium was replaced every time. The samples were analyzed for drug content against 0.1N HCl as a blank at wavelength of 224.6nm using double beam UV visible spectrophotometer.

Results and Discussion

Preformulation study:

UV spectrum of Venclafaxine HCl in0.1N HCl showed that the drug had λmax of 224.6nm. It is shown in Fig 2.

DSC report showed that the Melting point of Venlafaxine HCl sample was 211.90. It is shown in Fig-3. The IR spectrum of venlafaxine HCl was shown to exhibit the characteristic peaks at 3100-3000cm^{-1} for C-H(aromatic) stretching,2850-2960 for C-H(aliphatic) stretching,1450-1010 cm^{-1} for C-H bending,1360-1180 cm^{-1} for N-C bending,1300-1100 cm^{-1} for O-CH3 group,1300-900 C-O,3400-3200 cm^{-1} for O-H group and 1200-800 for C-C stretching. It is given in fig 4. Fig-5, Fig-6 and Fig 7 are depicting the IR spectras of HPMC K100, PVP K30 and formulation. No significant differences were observed in the drug and excipients interaction spectrums so minimum chance of interaction between venlafaxine HCl and other excipients.

Quality control test for granules and the floating tablets was performed and the results are depicted in Table 2 and Table 3 respectively. The hardness of the tablets is between 4-6 kg/cm². The invitro dissolution release study indicated for 8 hrs is given in Fig 8. Treatment of the dissolution data for type of release is investigated for Higuchi, ZeroOrder and Koresmeyers peppas model. The results are given in Table 4.

The curve fitting result of the release rate profiles of the formulation gives an idea on the release rate and mechanism of drug release.In this study it was indicated that the most of the formulations follow the zero order release kinectics.Fitting of the release data to korsmeyer peppas model it was reported that the diffusion coefficient (n) was found to be more than 0.80 in most of cases.

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Table 1: STD curve of Venlafaxine HCL in 0.1N HCL

Concentration	Absorbance
0	0.0000
5	0.2353
10	0.3971
15	0.6107
20	0.7578
25	0.9727
30	1.1177

Fig-1 Standard curve of Venlafaxine HCl

Standard curve of Venlafaxine HCL

$y = 0.037x + 0.028$
$R^2 = 0.997$
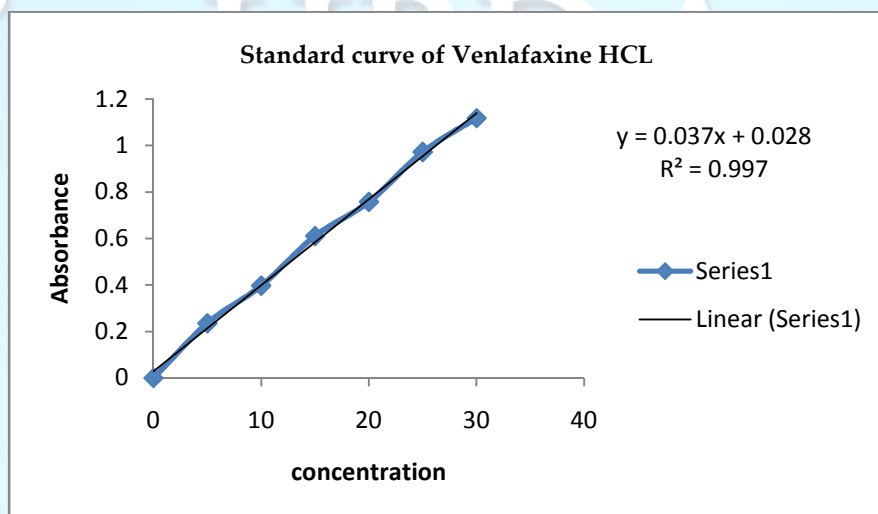
Table-2: Different Formulations of Venlafaxine HCL.

Iingredients	F1	F2	F3	F4
Drug(mg)	75	75	75	75
HPMC(mg)	60	80	90	100
sod.bicarb(mg)	60	60	60	60
Citric acid(mg)	12	12	12	12
PVP K30(mg)	27	27	27	27
Mg,stearate(mg)	6	6	6	6
Talc(mg)	5	5	5	5
Lactose(mg)	55	35	25	15
Total(mg)	300	300	300	300

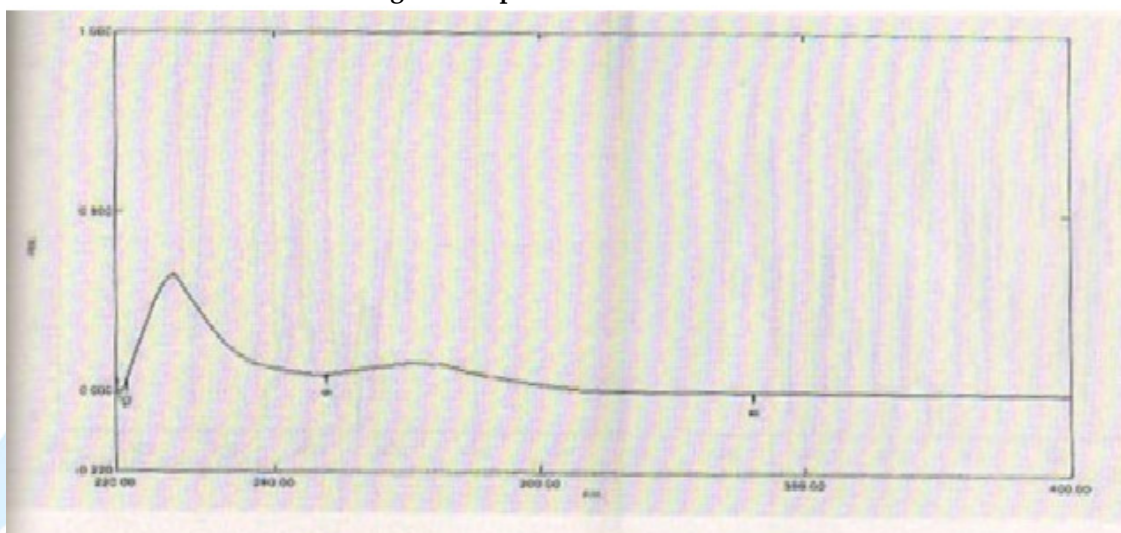**Fig-2: UV Spectrum of Venlafaxine**

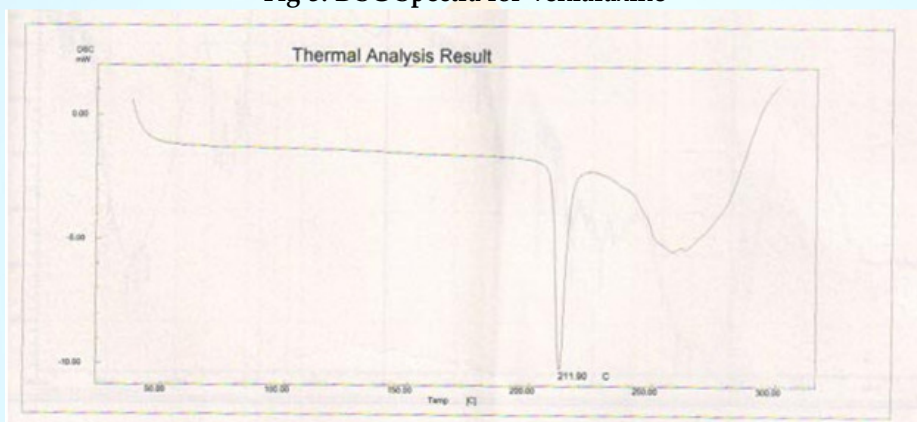
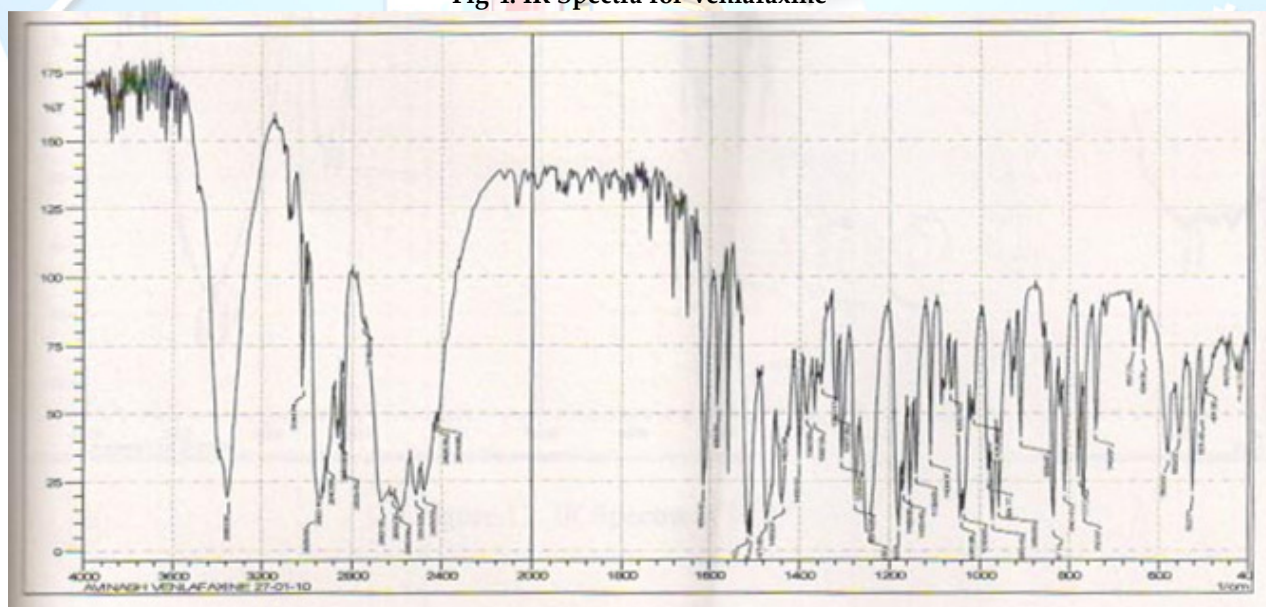**Fig-3: DSC Spectra for Venlafaxine**

Fig-4: IR Spectra for Venlafaxine

Fig-5: IR Spectra HPMC K100

Fig-6: IR Spectra PVP K30

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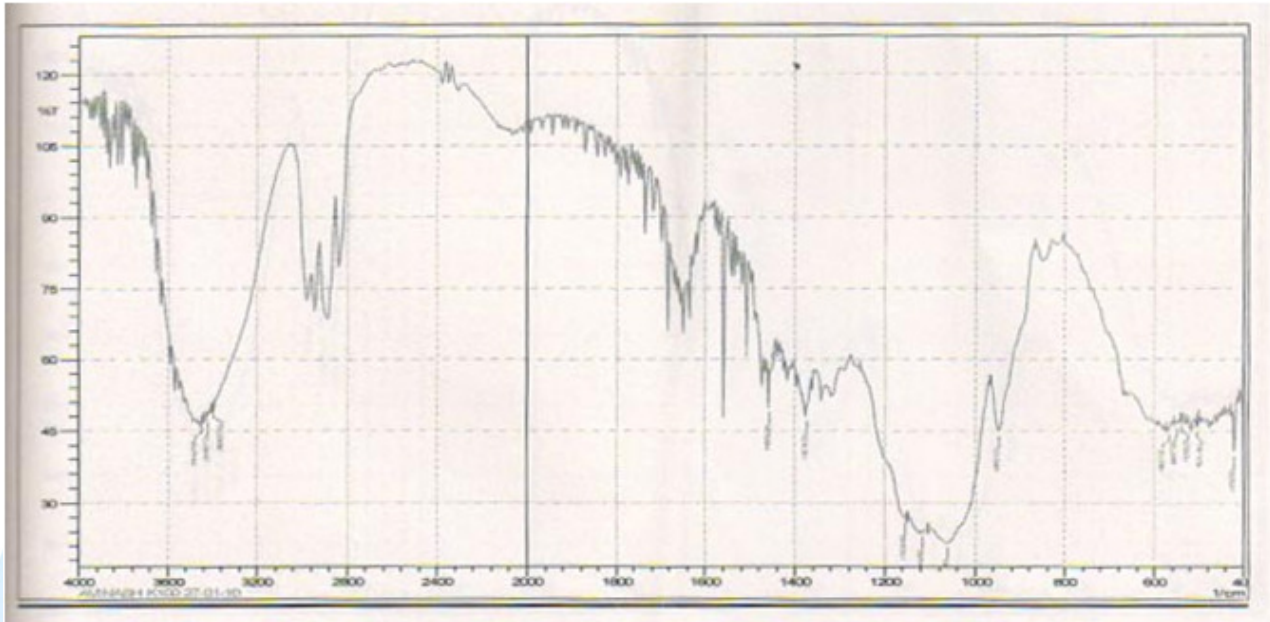
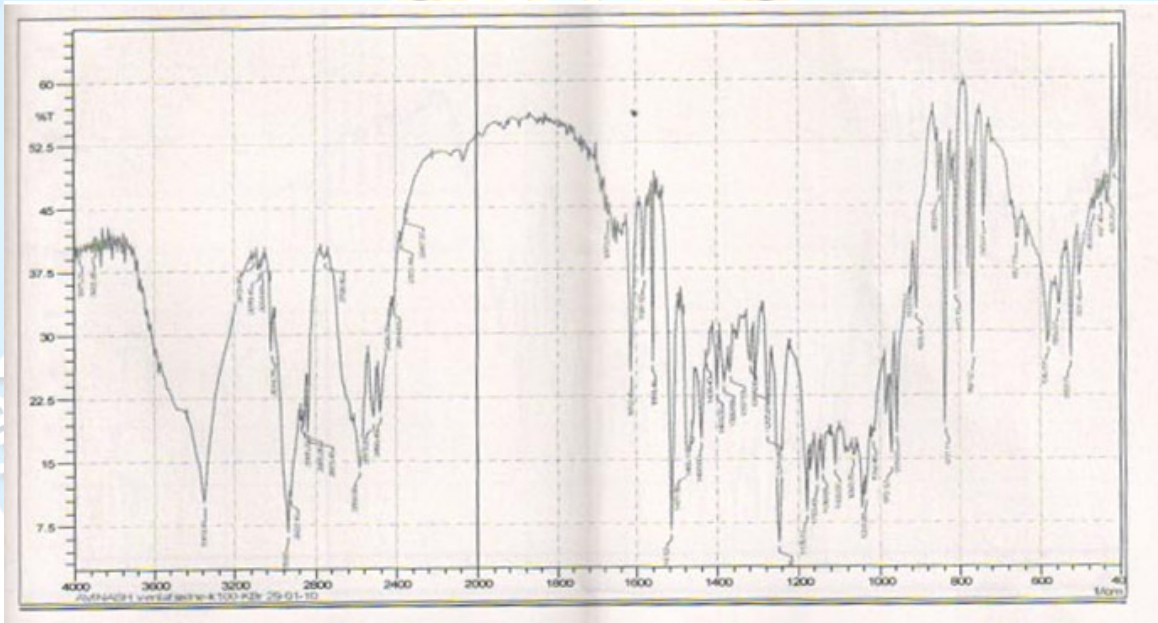**Fig-6: IR Spectra formulation**
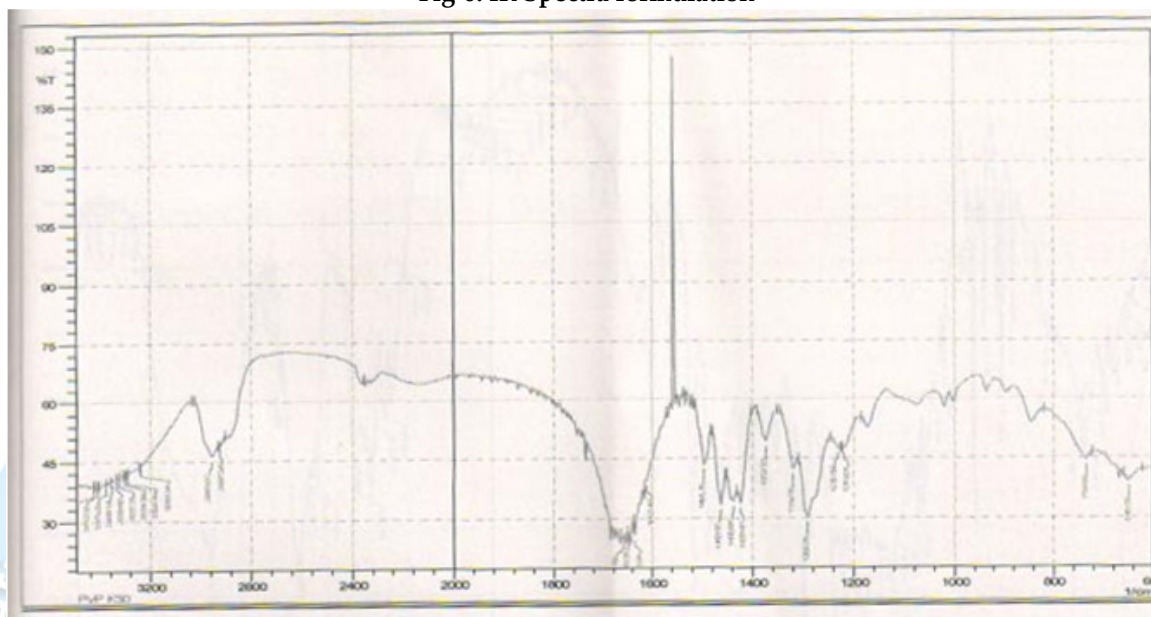
Table 2.Charaterization of granules

code	Angle of repose	Bulk density	Tapped density	Hausner ratio	carrs index
F1	27.149	0.521	0.667	1.331	21.89
F2	28.391	0.502	0.634	1.281	22.98
F3	26.566	0.495	0.651	1.316	24.03
F4	27.149	0.492	0.665	1.357	26.01

Table No.3.The tablet density was found to be uniform among different batches of floating tablets.

Code	Tapped density	% weight variation	Drug Content (Avg)	Average weight ± SD	Drug Content (Avg) ± SD	% Friability	Floating Lag Time in seconds	Floating Time in hours
F1	0.99	±2.59	25.06	309±2.59	25.06±0.34	< 1 %	08	09.18
F2	0.94	±4.17	24.58	288±4.17	24.58±0.25	< 1 %	07	09.10
F3	0.99	±2.25	24.94	311±2.25	24.94±0.31	< 1 %	06	13.52
F4	0.96	±4.73	24.87	296±4.73	24.87±0.22	< 1 %	12	13.16

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Fig-7 Dissolution study of venlafaxine gastro-retentive tablets

% CR indicates % Cumulative release.
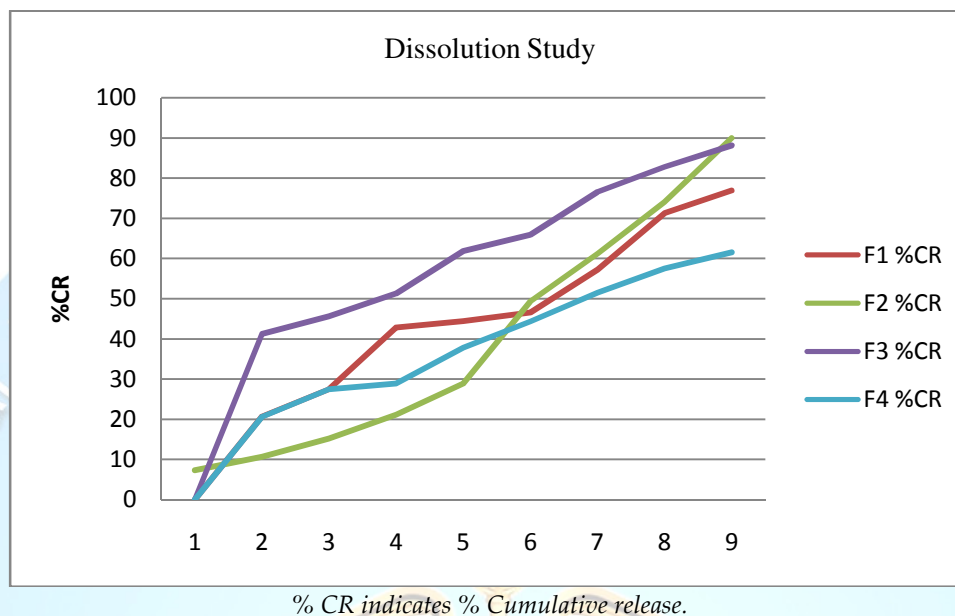
Table no.8 Dissolution data treatments of tablets

Batch	Zero order		Higuchi		Korsmeyer Peppas		
	Ko	r2	KH	r2	N	r2	Km
F1	7.354	0.0358	20.797	0.1012	0.857	0.9873	8.83
F2	8.76	0.1539	24.773	0.4352	0.806	0.9816	9.92
F3	8.672	1	24.533	0.2517	1	0.9778	6.24
F4	6.563	0.0737	18.559	0.2084	0.975	0.9875	7.26

Conclusion

The aim of the present study was to develop venclafaxine Hcl controlled release dosage form using gastro-retentive floating drug delivery systems which can effectively control the release of drug.The gastric retention time of Venlafaxine HCl can be increased by formulating it in a floating dosage form using optimum amount of HPMC, NaHCo3 and citric acid. The addition of gel-forming polymer HPMC and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve invitro buoyancy. The floating tablets were evaluated for uniformity of weight, hardness, and friability, drugcontent, invitrobuoyancy and dissolution studies.A lesser floating lag time and a prolonged floating time could be achieved by varying the amount of effervescent agent and polymer. The produced floating tablets exhibited good floating time and controlled drug release over a period of 8 hours. It was concluded that a floating tablet with good flow property and controlled release property can be obtained by optimizing amount of HPMC, sodiumbicarbonate and citric acid. The drug release from tablets was sufficiently sustained and Fickian transport of the drug from tablets was confirmed.Among these formulations of Venlafaxine HCL,F2 showed maximum release and proved to be best.

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