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RESEARCH ARTICLE

FORMULATION OF VENLAFAXINE HCL AS GASTRO-RETENTIVE TABLET USING DIFFERENT CONCENTRATION OF HPMC AND ITS EVALUATION

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ABSTRACT

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, G I transit time of dosage form, drug release from the dosage form and site of absorption of drugs. The gastro retentive drug delivery systems retains in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastro intestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. 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, F12 showed maximum release and sustained the action for the period and proved to be best.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, G I transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Drug delivery in oral conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. A beneficial drug delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site.(1,2,3,4)

Dosage forms that can be retained in the stomach are called gastro retentive drug delivery systems. The gastro retentive drug delivery systems retains in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastro intestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.(5,6,7)

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]

Floating drug delivery system is a more convenient and logical approach to prolong gastric residence time.[13,14,15,16]

MATERIALS

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

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METHODOLOGY

Preformulation study

The preformulation studies were performed for drug as well as polymers. These studies are preliminary identification test, bulk density, tapped density and compressibility index.

Identification test

Drug

Scanning of Venlafaxine Hydrochloride in 0.1N HCl**:**
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.

Drug study

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]

Excipients study

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]

Drug and excipients interaction study

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.

Standard curve of Venlafaxine HCL

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 absorbance 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.

Observation

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.

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

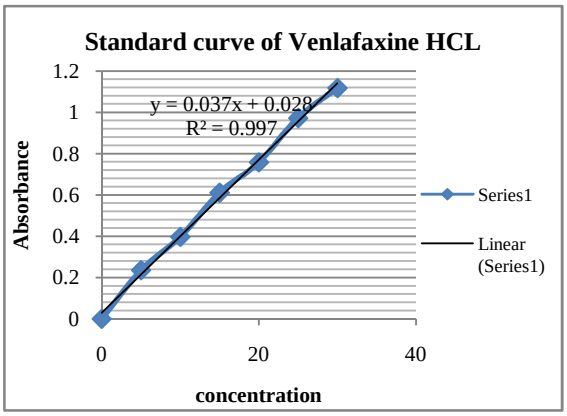

Figure No.1 Standard curve of Venlafaxine HCl

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.

ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug(mg)	75	75	75	75	75	75	75	75	75	75	75	75
HPMC(mg)	60	80	90	100	60	80	90	100	60	80	90	100
sod.bicarb(mg)	30	30	30	30	40	40	40	40	50	50	50	50
Citric acid(mg)	12	12	12	12	12	12	12	12	12	12	12	12
PVP K30(mg)	27	27	27	27	27	27	27	27	27	27	27	27
Mg,stearate(mg)	6	6	6	6	6	6	6	6	6	6	6	6
Talc(mg)	5	5	5	5	5	5	5	5	5	5	5	5
Lactose(mg)	85	65	55	45	75	55	45	35	65	45	35	25
Total(mg)	300	300	300	300	300	300	300	300	300	300	300	300

Evaluation

Characterization of Granules

Angle of repose

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^{0}=h/r where h is the height of pile and r is the radius of the pile

Bulk density

Granules were poured gently through a glass funnel into 50ml graduated cylinder. Bulk density was calculated.

Bulk density=M/Vo where M is the mass of powder and Vo is the bulk volume

Tapped density

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

Carrs index

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

Hausner ratio

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

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

Hardness

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.

Friability

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

Drug Content

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
Identification test

Drug

Scanning of Venlafaxine HCl in 0.1N HCl:
UV spectrum of Venclafaxine HCl in0.1N HCl showed that the drug had λmax of 224.6nm.

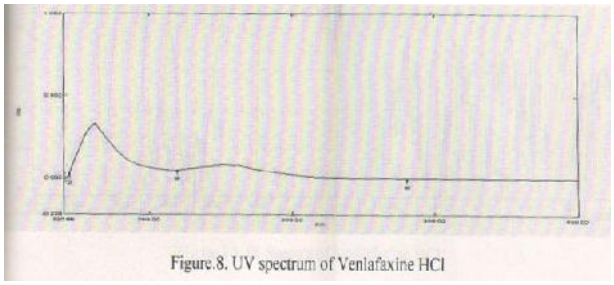

Figure No.2 UV spectrum of Venlafaxine HCl

DSC analysis

DSC report showed that the Melting point of Venlafaxine HCl sample was 211.90.

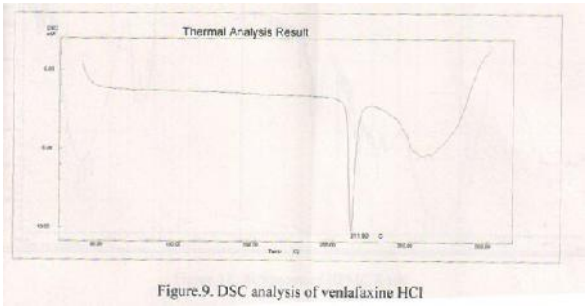

Figure No.3 DSC analysis of Venlafaxine HCl

Drug Study

The 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.

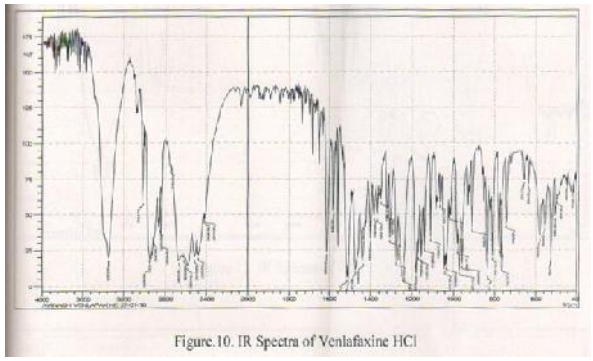

Figure No.4 IR spectra of Venlafaxine HCl Excipients study

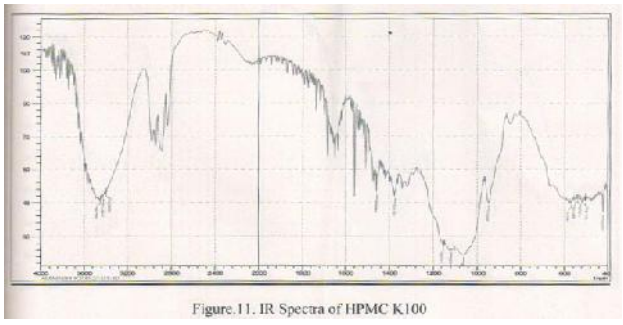

Figure No.5 IR spectra of HPMC K100

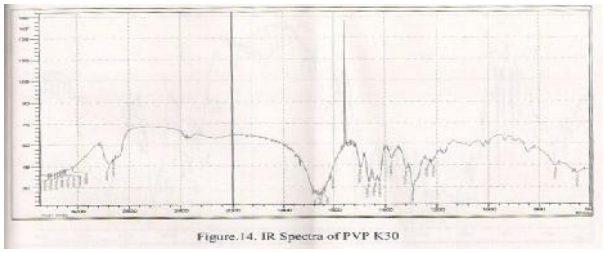

Figure No.8 IR spectra of PVP K30

Drug-Excipients interaction study

No significant differences were observed in the drug and excipients interaction spectrums so minimum chance of interaction between venlafaxine HCl and other excipients.

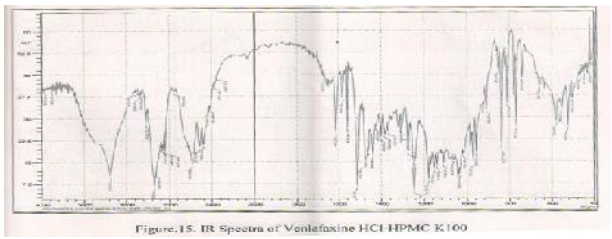

Figure no.9 IR spectra of Venlafaxine HCl- HPMC K100

Evaluation

Charaterization of granules

The prepared granules of different formulations were evaluated for angle of repose, bulk density, tapped density, Hausnerratio, and carr index.

Table no.2 Charaterisation of granule

code	Angle of repose	Bulk density	Tapped density	Hausner ratio	Carr index
F2	29.052	0.515	0.678	1.315	24
F3	29.744	0.505	0.656	1.299	22.97
F4	28.391	0.499	0.657	1.316	23.98
F5	27.758	0.522	0.66	1.266	22.86
F6	27.149	0.52	0.667	1.282	21.98
F7	27.758	0.518	0.663	1.281	21.99
F8	28.391	0.494	0.686	1.387	27.98
F9	26.566	0.506	0.682	1.349	25.91
F10	29.744	0.511	0.671	1.314	24.03
F11	27.149	0.499	0.666	1.333	24.97
F12	27.759	0.498	0.655	1.258	23.99

Characterisation of Tablets

Tablet density

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

Formulation	Tablet density	Results
F1	0.97	pass
F2	0.95	pass
F3	0.98	pass
F4	0.96	pass
F5	0.99	pass
F6	0.94	pass
F7	0.95	pass
F8	0.97	pass
F9	0.98	pass
F10	1	pass
F11	0.98	pass
F12	0.97	pass

Hardness

The hardness of all formulation was kept between 4 and 6 kg/cm.

Uniformity of weight

Table No.4 All prepared batches comply with the USP standards

Formulation	Average weight	%weight variation
F1	292	±3.42
F2	287	±5.22
F3	301	±5.99
F4	284	±4.22
F5	314	±1.59
F6	294	±2.72
F7	286	±4.55
F8	299	±3.01
F9	302	±3.64
F10	307	±1.95
F11	297	±6.06
F12	282	±6.74

Drug content

Table No.5 Drug content of different batches of tablet formulations

code	Drug Content				
	I	II	III	Average	SD
F1	25.42	25.13	24.93	25.16	±0.25
F2	24.15	24.95	24.43	24.51	±0.41
F3	24.62	24.86	24.77	24.75	±0.12
F4	24.91	25.9	25.26	25.36	±0.50
F5	25.83	24.65	24.7	25.06	±0.67
F6	24.66	24.85	25.35	24.95	±0.36
F7	25.25	25.64	24.56	25.15	±0.55
F8	25.61	25.75	25.45	25.6	±0.15
F9	25.91	25.48	25.23	25.54	±0.34
F10	24.49	25.36	24.88	24.91	±0.44
F11	24.78	24.43	25.12	24.78	±0.35
F12	25.64	24.8	24.7	25.05	±0.52

Friability

The percentage friability of different batches of tablets was found to less than 1%.All the batches of tablets were found to pass the friability test.

Study of Floating Properties

The floating lag time was found to be less than 15s and total floating time was found to be greater than 9h and less than 14h.

Table no.6 The floating lag time and total floating time of different formulations of venlafaxine HCL

Formulation	Floating lag time(seconds)	Floating time(hr)
F1	10	13.33
F2	14	10.23
F3	13	9.47
F4	26	10.04
F5	12	13.5
F6	17	11.28
F7	7	12.07
F8	17	11.54
F9	6	11.56
F10	14	13.3
F11	9	9.52
F12	8	13.27

Dissolution Study

The invitro drug release data of different batches of tablet formulations are shown in table no.6. The plots of % cumulative drug release v/s Time (hr) for tablet of different batches are given in figure no.6,7,8

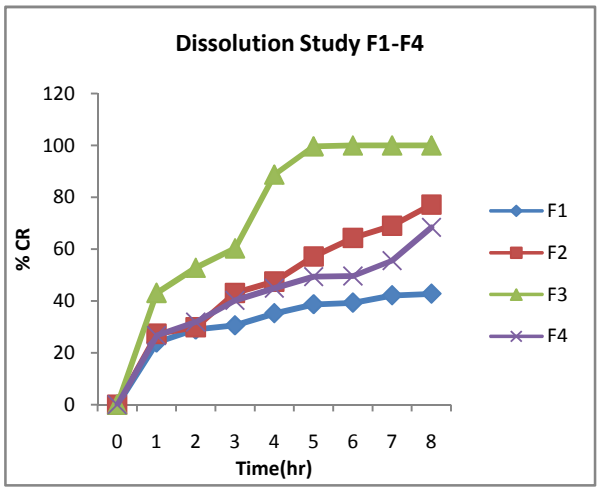

Figure no.6 Dissolution study F1-F4

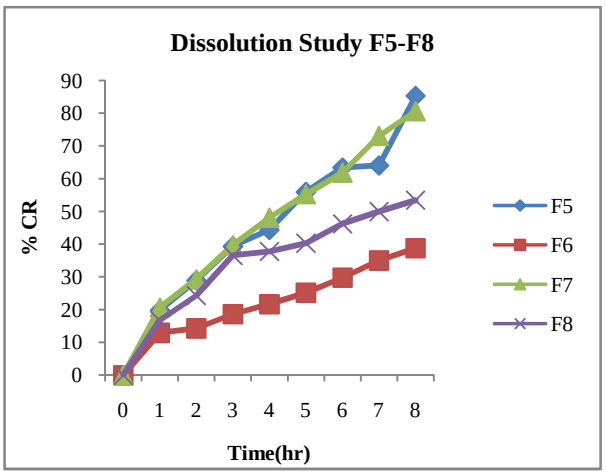

Figure no.7 Dissolution study F5-F8

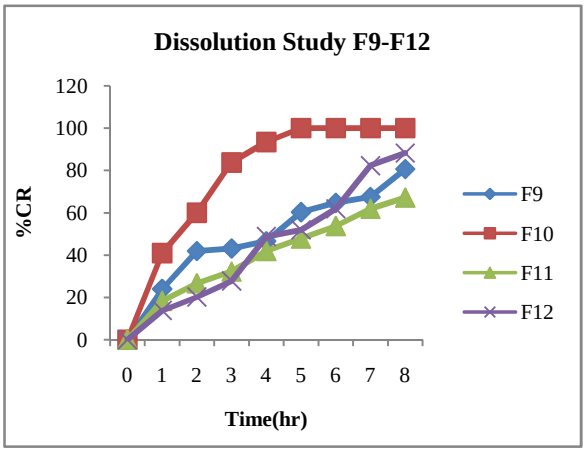

Figure no.8 Dissolution study F9-F12

Treatment of dissolution data with different model
The results of kinetic treatment applied to dissolution profiles of tablets shown in table no8

Time(hr)	F 1		F 2		F 3		F 4		F 5		F 6		F 7		F 8		F 9		F10		F11		F12
	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR	SD	%CR
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1	24	2.86	27.34	0.9	43.13	3.88	26.66	0.68	19.84	0.4	12.91	0.24	20.69	4.41	16.69	0.17	23.97	0.46	40.94	0.09	18.31	3.22	13.81
2	29.06	3.69	29.88	0.32	52.81	1.47	31.88	0.7	28.94	0.7	14.31	0	29.31	1.71	24.31	0.26	41.88	1.37	60	0.38	26.66	3.01	20.16
3	30.63	2.27	43.13	0.3	60.31	1.3	40.31	0.6	39.38	0.2	18.63	1.15	39.69	1.2	36.56	0.93	43.13	0.69	83.75	1.6	32.19	3.17	27.72
4	35.31	2.72	47.5	0.78	88.75	0.83	45	0.64	44.38	0.8	21.69	1.13	48.13	1.63	37.81	0.3	46.56	1.06	93.44	1.45	41.88	3.21	48.75
5	38.75	2.96	57.19	2.3	99.69	0.62	49.38	0.44	55.94	0.6	25.19	0.48	55.31	2.09	40.31	1.85	60.31	1.14	100	1.43	47.81	3.53	51.88
6	39.38	3.95	64.38	2.28	100	0.31	49.69	0.71	63.44	1.2	29.75	0.86	61.88	1.99	46.25	3.3	64.69	1.54	100	1.7	53.75	1.97	61.88
7	42.19	2.58	69.06	3.08	100	0.32	55.63	0.69	64.06	1.9	35	1.58	73.13	1.79	50	4.13	67.5	1.51	100	3.3	61.88	2.48	82.19
8	42.81	0.94	77.19	1.6	100	0.15	68.44	0.16	85.31	3.2	38.75	1.41	80.63	2.71	53.44	6.06	80.63	1.89	100	2.88	67.19	1.82	88.13

Table no.8 Dissolution data treatments of tablets

Batch	Zero order		Higuchi		Korsmeyer Peppas		
	Ko	r2	KH	r2	N	r2	Km
F1	4.0134	o.0209	11.35	0.0591	0.324	0.9952	48.65
F2	7.2365	0.0866	20.465	0.2449	0.856	0.9992	9.85
F3	14.954	0.0036	42.289	0.0102	0.138	0.8341	76.09
F4	6.416	0.0348	18.145	0.0984	1.285	0.9842	3.96
F5	8.3203	0.0226	23.529	0.0639	1.243	0.9966	4.1
F6	3.955	0.001	11.186	0.0028	1.166	0.9791	4.5
F7	8.672	0.0258	24.533	0.7296	0.066	0.8534	86.66
F8	5.333	0.0613	15	0.1734	1.328	0.9875	3.45
F9	7.823	0.0537	22.122	0.1519	0.989	0.9907	7.45
F10	23.36	1	66.062	2.828	1.558	0.9977	1.76
F11	7.002	0.0283	19.802	0.08	0.751	0.9965	11.65
F12	8.701	0.0453	24.606	0.1281	0.146	0.8911	74.59

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.

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,F12 showed maximum release and sustained the action for the period and proved to be best.

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