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FORMULATION, EVALUATION AND RADIOGRAPHIC STUDY OF STOMACH SPECIFIC FLOATING TABLETS CONTAINING VENLAFAXINE HYDROCHLORIDE FOR TREATMENT OF DEPRESSION

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Keywords:

Depression, Velnafexine hydrochloride, Floating tablets, Diffusion, X-ray studies

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ABSTRACT: Depression is a chronic, recurring, and potentially life-threatening illness. The present work is to formulate floating tablets of venlafaxine hydrochloride as this drug is used to treat depression. GIT absorption of venlafaxine hydrochloride is poor due to low aqueous solubility. Thus, an attempt was made to enhance it gastric residence time that will improve its dissolution profile. The floating tablets were prepared by direct compression method. The Fourier transform infrared spectroscopy revealed absence of any drug - polymer interactions. The floating tablets were evaluated for hardness, thickness, friability and drug content. The drug content of tablets was in range of 97.43 ± 1.56 to 98.71 ± 2.87%. The floating lag times of tablets for all batches were found in the range of 36.0 ± 1.1 to 68.0 ± 2.9 sec. The radiographic study of tablets containing barium meal showed that floating tablets remained buoyant for more than 12 h. The drug release from floating tablets followed Korysmer Pappas model. The results suggested that prepared floating tablets containing venlafaxine hydrochloride could enhance gastric residence time as remain buyout for long time and modulate the drug release.

INTRODUCTION: Controlled release drug delivery systems (CRDDS) provide drug release at predetermined and controlled rate. An important demand for the successful performance of oral CRDDS is that the drug should have good absorption throughout the gastrointestinal tract (GIT), preferably by passive diffusion, to ensure continuous absorption of the released drug. The pH dependent solubility and stability level of a drug plays an important role in its absorption.

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A drug must be in a solubilized and stable form to successfully cross the biological membrane, and it will experience a pH range from 1 to 8 as it travels through the GIT [1]. Drugs having site specific absorption are difficult to formulate as oral CRDDS because only the drug released in the area preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes to waste with negligible or no absorption [2].

Gastro retentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release medicament to the upper part of the gastrointestinal tract. A controlled release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs-

acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values. Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration [3].

HPMC, when used alone, may exhibit an initial burst release for very soluble drugs. This behavior has been attributed to the rapid dissolution of the drug from the surface near the surface of the matrix, while the polymer undergoes hydration to form a protective gel layer. HPMC and Pullulan gum have been used for modulating drug release and to prevent the burst release of highly soluble [4]. Venlafaxine hydrochloride, is a highly water soluble and structurally novel antidepressant for oral administration. It is a dual serotonin and norepinephrine reuptake inhibitor. It inhibits the serotonin transporter at 30 fold lower concentrations than norepinephrine transporter, respectively [5]. It display differential effects on norepinephrine reuptake in healthy versus depressed patients. It is highly soluble in 0.1 N HCl and it decreases with increasing pH over the physiological range. The half-life of venlafaxine hydrochloride is 5 ± 2 h, necessitating the administration, two or three times daily to maintain adequate plasma drug concentration [6].

The purpose of this study was to improve the release profile of velnafexine HCl in the stomach in a controlled manner to improve the therapeutic benefit of selected drug. It is hypothesized the improved bioavailability might be due to increased gastric residence time and swelling and hydration nature of polymers used.

MATERIALS AND METHODS:

Materials: Venlafaxine HCl was received as gift sample from Torrent Pharmaceuticals, Ahmadabad. HPMC K100M was purchased from Fine Chem. Labs., Mumbai. Pullulan gum was received as gift sample from Aurobindo Pharmaceuticals Ltd., Hyderabad. Microcrystalline cellulose, sodium bicarbonate, citric acid, hydrochloric acid, magnesium stearate, and talc were purchased from CDH Pvt. Ltd., Mumbai, India.

Preparation of Venlafaxine HCl Floating Tablets: The gastroretentive floating tablets of Venlafaxine HCl were prepared using swellable polymer, like Pullulan Gum and HPMC K100M with sodium bicarbonate ($NaHCO_3$) and citric acid as gas generating agent, MCC as diluents / binder, magnesium stearate as lubricant and talc as glidant[7]. The drug and excipients were passed through sieve no. 44 prior to the preparation of the dosage form. The entire ingredients were weighed separately and mixed thoroughly for 10 min to ensure uniform mixing in geometrical ratio. The tablets were prepared by direct compression technique using single punch hand operated tablet punching machine. Tablets (250 mg) were prepared in a total of nine batches of formulation. The prepared tablets were then evaluated for the following post compression parameters [8, 9].

TABLE 1: COMPOSITION OF VARIOUS GASTRORETENTIVE FORMULATIONS

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxine HCl	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5	37.5
Pullulan gum	37.5	75	112.5	37.5	75	112.5	37.5	75	112.5
HPMC K100 M	20	20	20	20	30	30	30	30	30
Sodium bi carbonate	25	50	50	50	50	25	75	25	25
Citric acid	10	10	10	10	10	10	10	10	10
MCC	115	52.5	15	90	42.5	30	55	67.5	30
Mg. stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of Floating Tablets:

Pre-Compression Evaluation: Bulk Density: A known amount of sample was carefully introduced in a graduated cylinder. The cylinder was dropped onto a hard wooden surface three times from a height of 1 inch at two second intervals. The bulk

density was then calculated by dividing the weight of sample in grams by final volume in cm^{10}.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Volume of powder}} \times 100$$

Tapped Density: Tapped Density was determined by mechanical taping of the measuring cylinder containing an amount of sample. The cylinder achieved the mechanical tapping operated for a fixed number of taps (100) until the bed volume reached a minimum. The tapped density was computed as:

$$\text{Tapped density} = \frac{\text{Mass of powder}}{\text{Volume of powder after tapping}}$$

Carr's index (% Compressibility): It indicated the ease with which a material can be induced to flow and expressed in percentage. It was calculated by the following formula:

$$\text{Carr's index \%} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio:

$$\text{Hausner's ratio} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

Angle of Repose: Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method.

$$\tan \theta = h/r$$

$$\text{Hence, } \theta = \tan^{-1} h/r$$

Where θ is the angle of repose, h is the height of cone and r is the radius of base

Post - Compression Evaluation:

Hardness: The tablet hardness was determined by using Monsanto hardness tester and expressed in kg/cm^2.

Thickness: It was determined by using digital Vernier caliper and expressed in mm.

Friability: Twenty tablets were weighed, rotated for 4 min at 25 rpm in Roche friability apparatus. Dedusted tablets were reweighed and the percentage of weight loss was calculated and expressed in percentage.

$$\text{Friability \%} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation: Weight variation test was performed by weighing 20 tablets individually, calculating the average weight and comparing individual weight to the average weight. It was expressed in % w/w.

Drug Content: A single tablet was dispersed in 100 ml of pH 1.2 HCl buffer, filtered, diluted and analyzed for drug content at 223 nm using UV-Visible spectrophotometer.

***In vitro* Buoyancy:** The *in-vitro* buoyancy was determined by floating lag time. The tablets were placed in a 100 ml capacity beaker which contains SGF. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT) [11].

Swelling Index: The swelling index of tablets was determined by placing a tablet in a 100 ml capacity beaker which contained SGF at room temperature up to 12 h. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated using equation [12].

$$\text{Swelling Index} = \frac{W_t - W_0}{W_0} \times 100$$

Where W_0 is the initial weight of tablet and Wt is the weight of tablet at time t.

***In-vitro* Drug Release Study:** It was performed by using USP type II apparatus at 100 rpm and in 900 ml SGF as dissolution media maintained at 37 ± 5ºC. One tablet (250 mg) equivalent to 37.5 mg of drug was placed in the basket. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals which was replaced with fresh dissolution medium of same quantity to maintain sink condition. Absorbance of these solutions was measured at 223 nm using UV/Visible double beam spectrophotometer. Cumulative percentage of drug release was calculated [13, 14].

Kinetics of Drug Release:

Zero - Order Release Kinetics: Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems.

$$Q = Q_0 + K_0t$$

Where Q was the amount of drug released or dissolved (assuming that release occurs rapidly after the drug dissolves), Q_0 was the initial amount of drug in solution and K_0 was the zero order release constant. A plot of the percent of drug released against time will be linear if the release obeys zero-order kinetics. The value of release rate constant k_0 was obtained in each case from the slope of cumulative percent drug released versus time plot.

First - Order Release Kinetics:

$$\log Q_t = \log Q_0 + \frac{k_1 t}{2.303}$$

The first-order equation described the release from systems where the rate was concentration dependent. Where Q_0 was the initial amount of the drug, time 't' in minutes and k_1 described the dissolution rate constant for first-order release kinetics. A plot of the logarithm of cumulative percent of drug remained against time would be linear if the drug obeyed first-order release kinetics. Values of release rate constant k_t were obtained in each case from the slope of the log cumulative percent of drug remained versus time plots.

The Simplified Higuchi Model:

$$Q(t) = k_H t^{1/2}$$

Where Q (t) was the percent of drug dissolved, time 't' in minutes, k_H was the dissolution rate constant for square root of time kinetics in percent drug dissolved $min^{-½}$. A plot of the fraction of drug released against square root of time would be linear if the release obeyed Higuchi equation.

Values of release rate constant k_H were obtained in each case from the slope of the cumulative percent of drug released versus square root of time plots.

Korsmeyer-Peppas Model: Korsmeyer *et al*., (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas' model.

$$Mt / M\infty = Kt^n$$

Where $Mt / M\infty$ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of n characterizes the release mechanism of drug. To study the release kinetics, data obtained from *in vitro* drug release studies. The values of the release exponent (n) and the kinetic constant (k) were determined in each case from the slope and y-intercept of logarithmic plot of cumulative percent of the drug released versus time respectively [15].

***In vivo* Evaluation:**

Preparation Dosage Form for *in vivo* Studies: The optimized formulations which showed good *in-vitro* buoyancy and sustained release behavior were finally selected for *in-vivo* study (*i.e.* radiography). The drug in selected formulation was replaced with the same amount of barium sulphate while all other ingredients were kept constant. These formulations were analyzed for their physical properties. The analysis confirmed that the developed dosage form was similar to those containing drug [16].

***In vivo* Studies:** The experimental protocol to carry out *in-vivo* radiographic studies were reviewed and approved by the Institutional Animals Ethical Committee of NKBR College of Pharmacy and Research Centre, Meerut, (Registration no. 1420/PO/a/11/CPCSEA). The *in-vivo* radiographic studies were conducted in young and healthy male albino rabbits weighing 2.0 to 2.2 kg. The animals were kept under standard conditions (temperature 25 ± 2 ºC). Rabbits were kept for one week in animal house to acclimatize them and were fed a fixed standard diet. The 4 healthy male albino rabbits were used to monitor the *in-vivo* transit behavior of the prepared dosage form (*i.e.* floating microspheres and floating tablets). None of the animal had symptoms or past history of gastro-intestinal (GI) disease. In order to standardize the conditions of GI motility, the animals were fasted for 12 h prior to the commencement of each experiment.

In each experiment, the first radiographic image of the animal subjects was taken to ensure the absence of radio-opaque material in the GIT. One of each dosage form prepared for radiography was orally administered to rabbits with sufficient amount of water. During the study the rabbits were not allowed to eat, but water was available *ad libitum*.

For radiographic imaging, the legs of the rabbit were tied over a piece of plywood (20 × 20 inch), and location of the formulation in the stomach was monitored by keeping the subjects in front of X-ray machine (Allengers, Bharat Electricals, India, Model no. E 080743). The distance between the source of X-rays and the object was kept same during the imaging process. Gastric radiography was done at the intervals of 1h, 2h, 4h and 6h. In between the radiographic imaging, the animals were freed and allowed to move and carry out normal activities but were not allowed to take any food [17].

RESULTS AND DISCUSSION:

Preformulation Studies:

Spectrophotometric Scan of Venlafaxine HCl:

Validation of λ_{max}: The samples containing different concentration of the drug were run and overlain spectra describing the reproducibility of the λ_{max} (earlier scanned) was obtained that confirmed and validated the process.

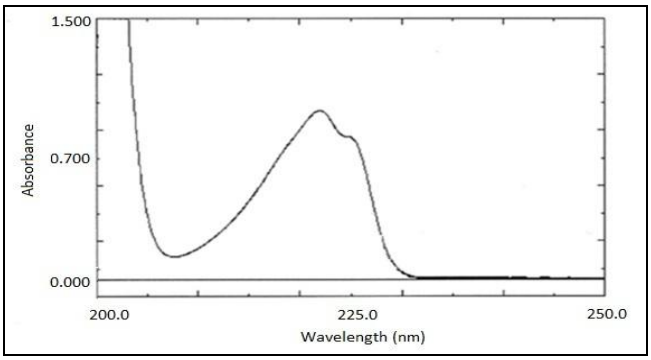

FIG. 1: SPECTROPHOTOMETRIC SCAN OF VENLAFAXINE HCl

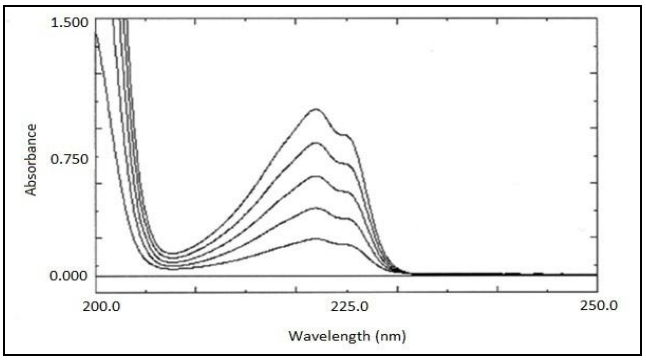

FIG. 2: OVERLAIN SPECTRA OF VENLAFAXINE HCl

Compatibility Studies:

FTIR Spectra of Venlafaxine HCl Pure Drug: The compatibility was studied with the spectra produced with drug + polymer combination comparing individual spectrum of each drug / polymer.

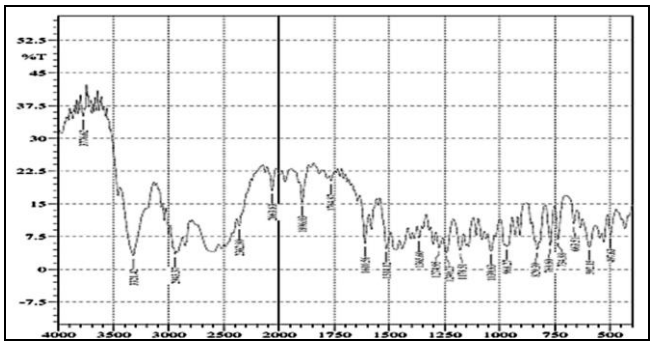

FIG. 3: FTIR SPECTRA OF VENLAFAXINE HCl PURE DRUG

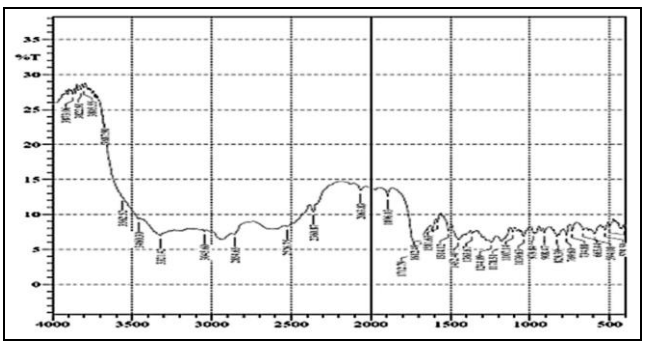

FIG. 4: FTIR SPECTRA OF FORMULATION BLEND

TABLE 2: IR VALUES OF VELNAFEXINE HYDROCHLORIDE

S. no.	Functional group	Reported values	Actual values
1	OH	3300-3400	3321
2	C_6H_5	1500-1600	1514
3	Aliphatic CH	2800-3000	2943
4	C-O-C	1000-1200	1039

Evaluation of floating tablets:

Pre compression evaluation: The prepared formulation blends (F1 - F9) were evaluated for various pre-compression parameters *i.e.* angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

TABLE 3: FLOW PROPERTIES OF FORMULATION BLENDS (F1 - F9)

Batch code	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hausner's ratio	Angle of repose (θ)
F1	0.50 ± 0.03	0.63 ± 0.01	20.63	1.26	30.12 ± 1.12
F2	0.51 ± 0.08	0.61 ± 0.06	16.40	1.19	25.26 ± 0.91
F3	0.53 ± 0.02	0.65 ± 0.02	18.46	1.22	28.10 ± 1.76
F4	0.50 ± 0.01	0.59 ± 0.03	15.25	1.18	23.54 ± 1.23
F5	0.49 ± 0.04	0.60 ± 0.07	18.33	1.22	28.62 ± 1.47
F6	0.52 ± 0.01	0.62 ± 0.02	16.12	1.19	25.00 ± 0.82
F7	0.53 ± 0.02	0.64 ± 0.01	17.18	1.21	27.70 ± 1.22
F8	0.50 ± 0.04	0.61 ± 0.03	18.03	1.22	28.95 ± 1.11
F9	0.52 ± 0.05	0.63 ± 0.07	17.46	1.21	26.85 ± 1.45

Post Compression Evaluation: Nine batches of floating tablets were prepared by direct compression technique and evaluated for post compression parameters such as hardness, thickness, friability, weight variation, diameter, floating lag time, total floating time, swelling index and the results of different evaluation parameters for F1 - F9 were as tabulated below [18].

TABLE 4: POST-COMPRESSION EVALUATION OF FORMULATIONS F1 - F9

Evaluation Parameters	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness (kg/cm^2)	5.5 ± 0.22	5.75 ± 0.52	5.8 ± 0.43	6.3 ± 0.22	6.2 ± 0.67	6.5 ± 0.76	5.75 ± 0.64	5.8 ± 0.11	6.3 ± 0.47
Thickness (mm)	2.75 ± 0.23	2.83 ± 0.53	2.8 ± 0.56	2.85 ± 0.50	2.95 ± 0.35	2.78 ± 0.34	2.88 ± 0.73	2.81 ± 0.12	2.88 ± 0.62
Diameter (mm)	8.05 ± 0.36	8.04 ± 0.13	8.03 ± 0.45	8.04 ± 0.76	8.05 ± 0.56	8.05 ± 0.76	8.04 ± 0.33	8.03 ± 0.67	8.04 ± 0.47
Friability (%)	0.63 ± 0.08	0.57 ± 0.02	0.61 ± 0.06	0.64 ± 0.02	0.54 ± 0.08	0.63 ± 0.06	0.53 ± 0.07	0.6 ± 0.05	0.61 ± 0.04
Wt. variation (mg)	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Drug content (%)	98.22 ± 1.89	97.43 ± 2.01	98.71 ± 2.87	97.43 ± 1.56	98.49 ± 1.87	98.23 ± 1.89	97.52 ± 1.76	98.6 ± 1.78	98.45 ± 1.56
Floating lag time (sec)	36.0 ± 1.1	40.0 ± 1.7	68.0 ± 2.9	45.0 ± 1.5	50.0 ± 1.9	48.0 ± 0.9	52.0 ± 1.2	57.0 ± 1.6	55.0 ± 1.4
Total floating time (h)	12.2 ± 0.2	18.6 ± 0.9	23.2 ± 1.2	20.4 ± 0.65	24.6 ± 1.3	22.8 ± 1.6	24.2 ± 0.8	24.2 ± 0.9	24.0 ± 0.8
Swelling Index (%)	55.0 ± 1.2	57.0 ± 1.8	65.0 ± 2.5	68.0 ± 2.8	70.0 ± 1.2	67.0 ± 2.3	60.0 ± 2.1	75.0 ± 2.3	70.0 ± 1.9

It can be seen that all the formulations had intercept values greater than 0.5 and less than 1, which confirms that the release mechanism of venlafaxine HCl from the floating tablets in acidic media (pH 1.2) was Fickian diffusion with swelling [19, 20].

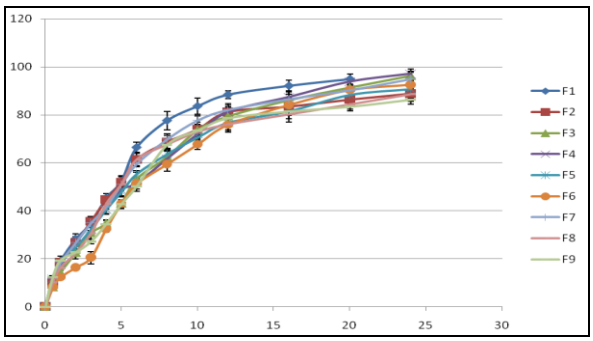

FIG. 5: DRUG RELEASE DATA OF FORMULATION F1 - F9

Release Kinetics Data of Floating Tablets:

TABLE 5: RELEASE KINETICS DATA OF FLOATING TABLETS

Formulation Code	Zero Order	First Order	Higuchi Model	Korsmeyer Pappas Model
F1	0.8669	0.8921	0.9622	0.9734
F2	0.8604	0.8708	0.9585	0.9694
F3	0.8849	0.8976	0.9675	0.9777
F4	0.9026	0.9121	0.9785	0.9871
F5	0.8801	0.8988	0.9619	0.957
F6	0.8684	0.8743	0.9619	0.9747
F7	0.8349	0.8566	0.9416	0.9653
F8	0.7911	0.8021	0.9121	0.9361
F9	0.8156	0.8266	0.9159	0.9444

***In vivo* Evaluation:** *In-vivo* radiographic study done on $BaSO_4$ loaded floating tablets showed that these tablets retained in the stomach for more than 6 h.

The position of tablet was found to be changed with time. It was also observed that the size of tablet was relatively bigger in radiographic image taken after three hour than that of taken after 1 h. It may be because of swelling of matrix in stomach fluid.

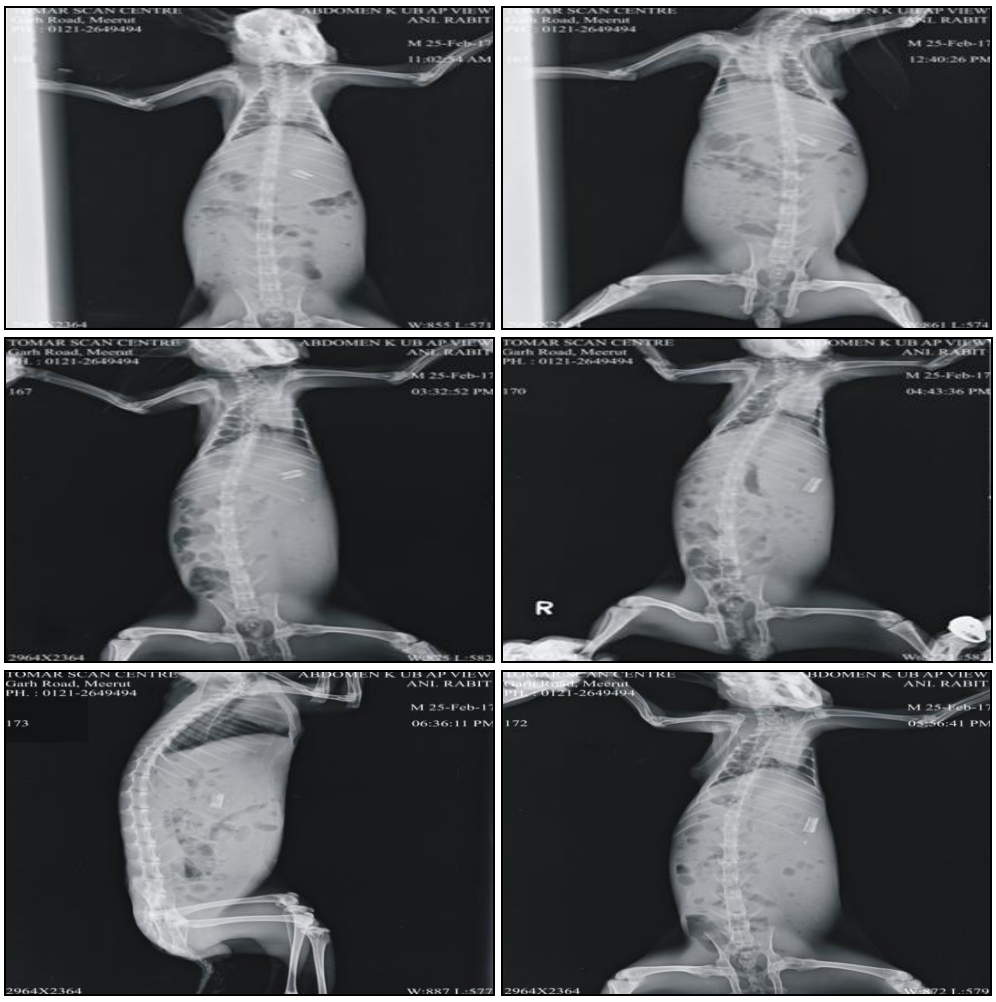

FIG. 6: RADIOGRAPHIC IMAGES SHOWING THE PRESENCE OF $BaSO_4$ LOADED FLOATING TABLET IN THE STOMACH AT 0, 2, 4, 6, 8, 10 h

CONCLUSION: The present study was aimed to develop the floating tablets of venlafaxine hydrochloride using HPMC K 100M and Pulllulan gum as carriers. Developed formulation gave satisfactory results for various evaluations for tablets like hardness, weight variation, floating lag time, and uniformity of content. *In vitro* dissolution studies of the optimized formulation showed the continued release for 24 h, followed by the Fickian diffusion. An *in vivo* study indicated long gastric residence time by the floating principle and was considered desirable for improving the bioavailability of the drug. Developed sustained release oral formulation would be a significant advantage for the patient and may result in fewer side effects due to reduction of the blood concentration fluctuations, especially in long-term therapy. Based on the results obtained from this study, it is hoped that further research with a variety of natural gum will lead to the development of more effective floating drug delivery systems. However, further clinical studies are needed to assess the utility of this system for patients suffering from depression.

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CONFLICT OF INTEREST: The authors declared "no conflict of interest" in the manuscript.

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