ORIGINAL ARTICLE

Preparation and Characterization of Floating Tablets of Venlafaxine Hydrochloride: An Approach for Depression Treatment

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Abstract

Objective: The present work is to formulate floating tablets of venlafaxine hydrochloride as this drug is used to treat depression. Gastrointestinal tract 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. **Materials and Methods:** The floating tablets were prepared by direct compression method using HPMC K100M and Pullulan gum as polymer in different combinations. Sodium bicarbonate and citric acid are added to cause effervescence. The floating tablets were evaluated for hardness, thickness, friability, swelling index, and drug content. **Results:** The Fourier transform-infrared spectroscopy revealed the absence of any drug-polymer interactions. The drug content of tablets was in the range of 97.43 ± 1.56–98.71 ± 2.87%. The floating lag times of tablets for all batches were found in the range of 36.0 ± 1.1–68.0 ± 2.9 s. The drug release from floating tablets followed Korsmeyer-Peppas model. **Discussion and Conclusion:** 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.

Key words: Diffusion, floating tablets, pullulan gum, surface plot, venlafaxine hydrochloride

Key Messages: The aim of this study was to reduce the dosing frequency of the drug and to improve the release profile of venlafaxine HCl. The floating tablets were prepared using HPMC K100M and Pullulan gum as polymer in different combinations.

INTRODUCTION

A modified-release dosage form is defined as one for which the drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized. Controlled drug delivery systems can include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance. An important demand for the successful performance of oral controlled-release drug delivery systems (CRDDSs) 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. 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]

Medicaments having site-specific absorption are difficult to formulate as oral CRDDS because only the medicament

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released in the area preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released medicament goes to waste with negligible or no absorption.[2]

Floating drug delivery systems are subjected to be retained in the stomach and release medicament in the upper part of the gastrointestinal tract. A controlled release drug delivery system with prolonged time in the stomach is of particular interest for drugs - those acting locally in the stomach; those having an absorption window in the stomach or in the upper part of small intestine; those are unstable in the intestinal or colonic environments; or those having low solubility at high pH values. Floating tablets have less bulk density as that of gastric fluids so remain buoyant in the stomach without affecting the gastric emptying rate for longer duration of time. While the tablet is floating on the gastric contents, the drug is released slowly at the desired rate from the tablets. 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 and Pullulan gum have been used for controlling drug release and to prevent the burst release of highly soluble. HPMC, when used alone, may exhibit an initial burst release for very soluble drugs. This behavior has been credited 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.[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 displays 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, 2 or 3 times daily to maintain adequate plasma drug concentration.[6]

The purpose of this study was to decrease the dosing rate of the drug and to improve the release profile of venlafaxine 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 obtained as a gift sample from Alkem Pvt., Ltd., Mumbai. 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 (P) Ltd., Mumbai, India.

Preparation of venlafaxine HCl floating tablets

The gastroretentive floating tablets of venlafaxine HCl were prepared using swellable polymer, such as 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 before 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 [Table 1]. The prepared tablets were then evaluated for the following post-compression parameters.[8,9]

Pre-compression evaluation

Compatibility studies between drug and excipients

The physical compatibility of venlafaxine HCl with various excipients was carried out with an aim to select suitable excipients for a stable and strong formulation. Fourier transform-infrared (FTIR) spectra of the drug and the drug with excipients were recorded in the range of 4000–400 cm^{-1}. Compatibility studies were performed using FTIR spectrometer. The FTIR spectrum of the pure drug and physical mixture of the drug and excipients were studied.

Bulk density and tapped density

A known amount of sample was taken into a 10 ml graduated measuring cylinder separately and the volume was noted down. The graduated measuring cylinder was tapped 100 times using USP bulk density apparatus (ETD 1020, Electrolab, Mumbai, India). The bulk density and tapped density were determined using the following formula:[10]

$$\text{Bulk density} = \frac{\text{mass of powder}}{\text{volume of powder}}$$

$$\text{Tapped density} = \frac{\text{mass of powder}}{\text{Tolume of powder after tapping}}$$

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:

Table 1: Composition of floating tablet formulations

Ingredients (mg/tab)	Formulation code								
	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

$$\text{Carr's index}(\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{TappedDensity}} \times 100$$

Hausner's ratio

It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density. It was calculated by the following formula:

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

Angle of repose

The flow property was determined by measuring the 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.

$\tan \theta = h/r$

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

Evaluation of floating tablets

Hardness

The resistance of tablet to chipping, abrasion or fracture under condition of storage, transportation, and handling before usage depends on its hardness. The tablet hardness was determined using Monsanto hardness tester and expressed in kg/cm^2.

Thickness

It was determined using digital Vernier caliper and expressed in mm. Tablet thickness should be controlled within a ± 5% variation of standard value.

Friability

The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked. 20 tablets were weighed, rotated for 4 minutes at 25 rpm in Roche friability apparatus. Dedusted tablets were reweighed, and the percentage of weight loss was calculated and expressed in percentage.

$$\text{Friability}(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X}100$$

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 total of 10 tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10 mg of venlafaxine HCl was dispersed in 100 ml of pH 1.2 HCl buffer, filtered, diluted, and analyzed for drug content at 223 nm using ultraviolet (UV)-visible spectrophotometer (LAB INDIA UV 3000+, Mumbai, India).

In vitro buoyancy

The tablets were placed in a 100 ml capacity beaker which contains pH 1.2 HCl buffer. 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 was determined by placing a tablet in a 100 ml capacity beaker which contained pH 1.2 HCl buffer

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 formula[12]:

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo} \text{ X } 100$$

$$Q(t) = K_H t^{½}$$

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 using USP type II apparatus at 100 rpm and in 900 ml pH 1.2 HCl buffer as dissolution media maintained at 37 ± 5°C. 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 (LAB INDIA UV 3000+, Mumbai, India). Cumulative percentage of drug release was calculated.[13,14]

Kinetics of drug release

Zero-order release kinetics

Zero-order release kinetics refer 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.

$$Q = Q_0 + K_0 t$$

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

The first-order equation described the release from systems where the rate was concentration dependent.

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

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

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.

$$Q(t) = K_H t^{½}$$

Where, Q (t) was the percent of drug dissolved, time "t" in minutes, and k_H was the dissolution rate constant for square root of time kinetics in percent drug dissolved $min^{-½}$.

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 were 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]

Response surface plots

The relationship between the dependent and independent variables was further elucidated using response surface plots. Figure 4 shows that the floating lag time of the tablets increased with an increase in the polymer concentration. This could be due to time taken by polymer to hydrate. Figure 5 suggests that all the polymer concentrations have a significant effect on drug release and control the release of drug from the microspheres. The increased density of the polymer matrix at higher polymer concentration results in an increased diffusion path length, which may decrease the overall drug release from the polymer matrix.[16,17]

Response surface methodology (RSM) has applications in the particular situations where several input variables potentially influence some performance measure or quality characteristic of the process. Thus, performance measure or quality characteristic is called the response. In the present study the effect of various independent variables such as concentration of alkali salt and gum concentration were investigated on buoyancy and percentage drug release.[17]

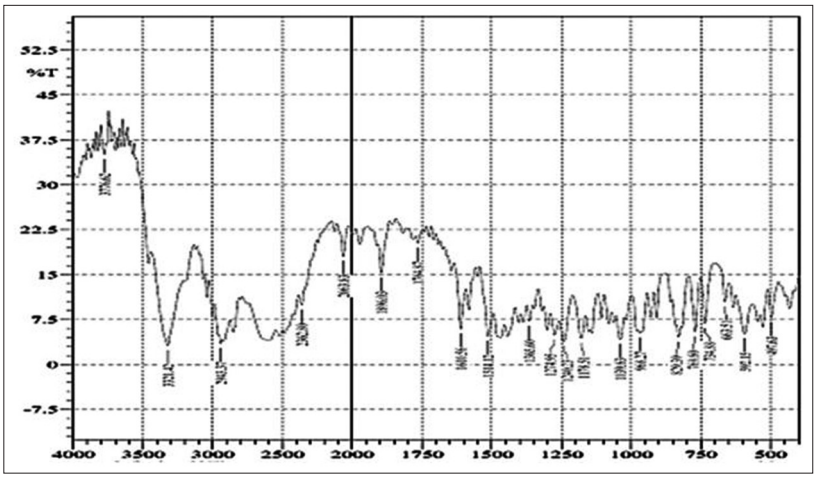

Figure 1: Fourier transform-infrared spectra of venlafaxine HCl pure drug

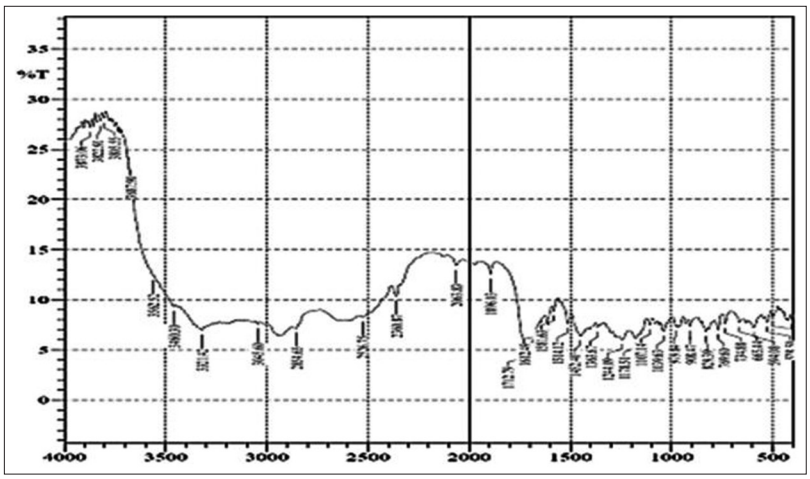

Figure 2: Fourier transform-infrared spectra of formulation blend

Table 2: IR values of venlafaxine hydrochloride

Functional group	Reported values	Actual values
OH	3300–3400	3321
C6H5	1500–1600	1514
Aliphatic CH	2800–3000	2943
C-O-C	1000–1200	1039

IR: Infrared

RESULTS AND DISCUSSION

Compatibility studies between drug and excipients

The compatibility was studied with the spectra produced with drug + polymer combination comparing individual spectrum of each drug/polymer [Table 2, Figures 1 and 2].

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].

Evaluation of floating tablets

Floating tablets were evaluated for post-compression parameters such as hardness, thickness, friability, weight variation, diameter, floating lag time, TFT, and swelling index. The results obtained are represented in Table 4.[18]

Release kinetics data of floating tablets

It can be seen that all the formulations had intercept values >0.5 and <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 [Figure 3 and Table 5].[17,19]

CONCLUSION

Floating tablets of venlafaxine hydrochloride were successfully developed using HPMC K 100M and Pullulan gum as carriers. Developed formulation gave satisfactory

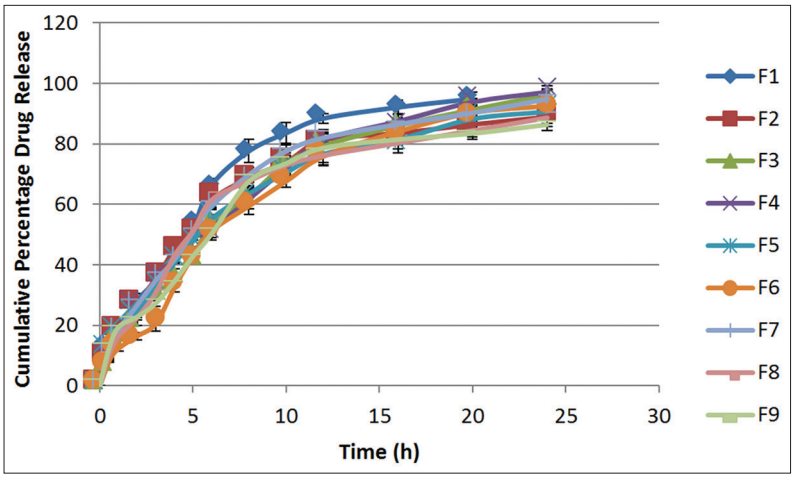

Figure 3: Release profile of venlafaxine hydrochloride from formulations F1-F9 in 0.1 N HCl (pH 1.2) at 37 ± 5°C (Data present mean ± standard deviation, $n = 3$.

Table 3: Flow properties of formulation blends (F1-F9)

BATCH CODE	Bulk Density (g/ml)	Tapped Density (g/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

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 (s)	36.0±1	40.0±2	68.0±3	45.0±1	50.0±2	48.0±1	52.0±1	57.0±1	55.0±1
TFT (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

Table 5: Release kinetics data of floating tablets

Formulation code	Zero order	First order	Higuchi Model	Korsmeyer-Peppas 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

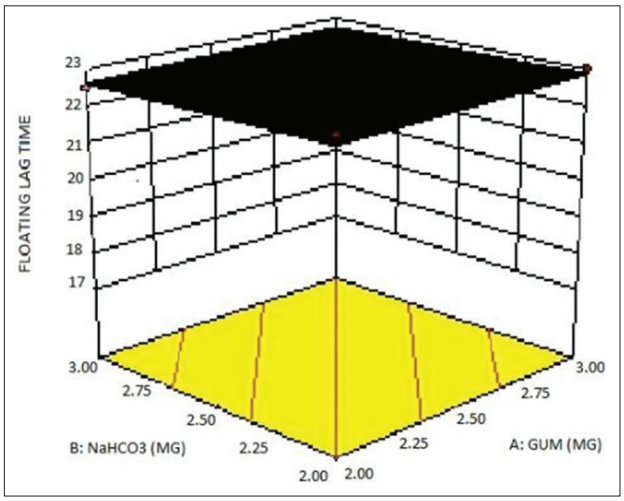

Figure 4: Response surface plots showing the influence of gum and NaHCO3 on floating lag time of floating tablets

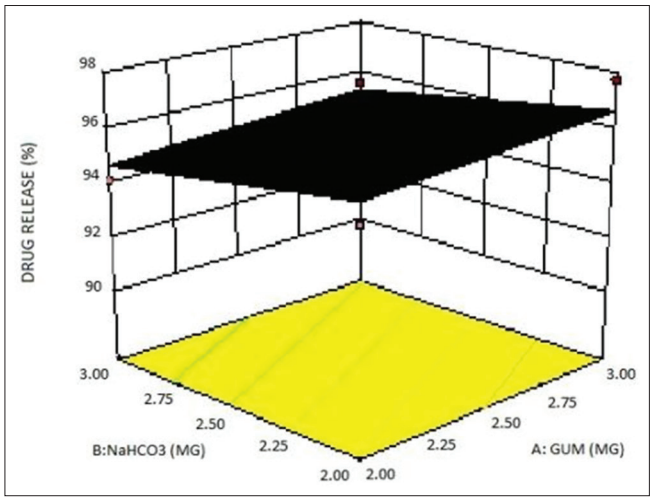

Figure 5: Response surface plots showing the influence of gum and NaHCO3 on percentage drug release of floating tablets

results for various evaluations for tablets such as 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. 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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