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Design and *In-Vitro* Evaluation of Floating Tablets of Gabapentin

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ABSTRACT

Gastro retentive system can remain in the gastric region for several hours and hence prolongs the gastric residence time of drugs. The present research work was an attempt to formulate and *in-vitro* evaluate gastro retentive floating drug delivery system containing Gabapentin in the form of tablets using polymer like HPMC K100M and sodium bicarbonate, citric acid as gas generating agent. A 3^2 factorial design was applied systematically; the amount of HPMC K100M (X_1) and amount of citric acid (X_2) were selected as independent variables. The floating lag time, percentage drug release at 6 hr (Q_6) and percentage drug release at 12 hr (Q_{12}) were selected as dependent variables. The tablets were prepared by direct compression method. The tablets were evaluated for the pre and post compression parameters such as weight variation, thickness, friability, hardness, drug content, *in-vitro* buoyancy studies, and *in-vitro* dissolution studies and results were within the limits. Hardness was found to be in the range 5.1±0.13 kg/cm^2 to 7.1±0.36 kg/cm^2, the percentage friability was in the range of 0.30% to 0.82% w/w, and tablets showed 99 to 101.10 %w/w of the labeled amount of Gabapentin indicating uniformity content. The *in-vitro* dissolution studies were carried out in a USP type-II apparatus in 0.1N HCl. Among all the formulations (GFT_1 to GFT_9) prepared, batch GFT_7 was the best formulation which showed buoyancy lag time 5 sec and the tablet remained buoyant for >12h. At all the strengths of the polymer tested HPMC K100M and citric acid gave relatively optimum release of gabapentin over 12 h when compared to other formulations. The tablets containing Gabapentin released 92.09 to 99.06% of drug release at the end of 12 hr by *in-vitro* drug release study. The *in-vitro* data is fitted in to different kinetic models and the best-fit was achieved with the Higuchi model. The optimized formulation GFT_7 followed zero order release kinetics followed by non-Fickian diffusion.

Keywords: Floating tablets, Gastric retention, Gabapentin, Factorial design, Anticonvulsant.

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INTRODUCTION

The goal of any drug delivery system is to provide a therapeutic amount of drug to proper site in the body to achieve promptly and then maintain a desired drug concentration.[1] The oral route is most preferable route for administration of the drug but it may have some disadvantages like slow onset of action or slow absorption. This problem can be overcome by using alternative dosages form or administrating the drug via other routes. While we are selecting a dosage form or route for administration of drug there are some parameters should be consider like stability and bioavailability of the formulation as well as active pharmaceutical ingredients.[2] The oral route of administration suffers with certain drawbacks mainly short residence time of the dosage form in the GI tract, unpredictable gastric emptying and degradation of the drug due to highly reactive nature of GI contents. Gastric emptying is a complex process and makes *in-vivo* performance of the drug delivery system uncertain. Formulation of floating drug delivery systems is a useful approach to avoid this variability with increased gastric retention time of the drug delivery system. Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 residence time and a better control of the fluctuation in plasma drug concentration. [3, 4]

Gabapentin, marketed under the brand name Neurontin among others, is a medication used to treat epilepsy, neuropathic pain, and hot flashes. [5] It is recommended as a first line agent for the treatment of neuropathic pain arising from diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain. [6] The exact mechanism of action is not well understood but its analgesic efficacy & safety has been demonstrated in physiological & pathological pain. Despite its structural similarity with GABA it does not act via mechanism related to GABA.[7] However, due to its short half-life (5-7h) and low bioavailability (60%), traditional immediate-release gabapentin solid dosage forms need to be administrated three times a day. Gabapentin is preferentially absorbed in duodenum through a suitable L-amino acid transport system. So gastric retained dosage is particularly beneficial for delivery of gabapentin since the dosage form would be able to keep the drug in the region of absorption window and show improved bioavailability by virtue of slower release rate that avoid saturation of carrier mediated

transport of conventional dosages. [8, 9]

MATERIALS AND METHOD

Gabapentin was obtained as gift sample from Marksans Pharma., Goa. Other excipients were used LR grade from reliable sources.

Pre-Formulation Studies/Standardization of Drug: Gabapentin [10]

Gabapentin was obtained as gift sample from Marksans Pharma., Goa. The drug was screened and tested for the following parameters as per monographic specifications. It was standardized as per USP and purity and identity were checked. Gabapentin was tested for the following-

Appearance:

Color of drug was observed visually

Solubility:

Solubility was checked in chloroform, ethanol, water, 0.1N NaOH and 0.1N HCl.

Loss on drying:

Drug (1gm) was weighed and dried in an oven at 100°C- 105°C to constant weight for 4 hours. The weight was again recorded.

Determination of Melting Point:

This was determined using open capillary method.

UV Spectra of Gabapentin:

The UV spectrum of Gabapentin was obtained using Shimadzu UV1800. Accurately weighed 100 mg of the drug was dissolved in sufficient quantity of 0.1N HCl and volume made up to 100 ml known as stock solution (1000 µg/ml). 10 ml of aliquot was withdrawn and volume was made up to 100 ml using 0.1N HCl to obtain the concentration of 100µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded.

Compatibility studies:

By FTIR spectroscopy:

In the preparation of tablet formulations, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Pre-formulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR spectroscopy was employed to ascertain the compatibility between Gabapentin and selected polymers. The pure drug, drug-polymers combinations and formulations were subjected to FT-IR studies. Potassium bromide, pure drug, and the polymers were heated to 105^0C for one hour to remove the moisture content if present in a hot air oven. Then in presence

of IR lamp, potassium bromide was mixed with drug and or polymer in 9:1 ratio. Grinding in smooth mortar can effect mixing. The mixtures were then placed in the sample holder of the instrument and the spectra were taken. The spectra were run from 4000 cm^{-1} to 800 cm^{-1} wave number. FT-IR spectrum of Gabapentin was compared with FT-IR spectrum of Gabapentin with polymer. The pure drug and the drug with excipients were scanned separately. Disappearance Gabapentin of peaks or shifting of peak in any of the spectra was studied.

Analytical Methods:

pH 1.2 Hydrochloric acid buffer:

Dissolve 8.5 ml of concentrated HCl in 1000 ml of distilled water.

Preparation of Standard Stock Solution:

Accurately, about 100 mg of Gabapentin was weighed and transferred to a 100 ml volumetric flask. The drug was dissolved in 100 ml of 0.1N HCl solution P^H 1.2 with shaking and then the volume was made up to the mark with buffer solution pH 1.2 to obtain a standard stock solution of a drug concentration, 1000 µg/ml. (stock solution I). From the stock solution I, pipette out 10 mL and placed into 100 ml volumetric flask. The volume was made up to mark with buffer solution to give a stock solution containing 100µg/ml (stock solution II).

Determination of analytical wavelength:

The resulting stock solution containing 100µg/ml was scanned between 200 to 400 nm on U.V. spectrometer.

Calibration curve for the Gabapentin:

Appropriate volume of aliquots from Gabapentin standard stock solution II were transferred to different volumetric flasks of 10 ml capacity. The volume was adjusted to the mark with distilled water to obtain concentrations of 5, 10, 15, 20, 25 and 30µg/ml. Absorbance spectra of each solution against distilled water as blank were measured at 210 nm and the graphs of absorbance against concentration were plotted and shown. The regression equation and coefficient of determination was determined.

Formulation Development: [11-13]

Formulation Design:

Formulation Design study is important for selection of appropriate excipients for preparation of tablets. The three different concentrations of HPMC K100 and citric acid were used for trial preparation of tablets. The trial batches of tablets were prepared by direct compression method using other commonly used excipients.

Method for Preparation of Floating Tablet:

The extended release floating tablets of Gabapentin was prepared by direct compression technique using various concentrations of HPMC K100M as release retarding polymer and citric acid as gas generating agent. Sodium alginate as a binder, Carboxymethyl cellulose sodium as a gel forming agent. The composition of various tablet formulation are given in Table 3. The ingredients were individually passed through sieve No.40# and mixed for 15 min. The mixture was lubricated with magnesium stearate and talc and then compressed into a tablet using a punches of machine (Karnawati Minipress-I).

Table 1: Composition of Gabapentin Floating tablet.

Sr.no	Ingredients(mg)	Weight per tablet (mg)								
		GFT_1	GFT_2	GFT_3	GFT_4	GFT_5	GFT_6	GFT_7	GFT_8	GFT_9
1	Gabapentin	300	300	300	300	300	300	300	300	300
2	HPMC K100M	75	100	125	75	100	125	75	100	125
3	Sodium Bicarbonate	40	40	40	40	40	40	40	40	40
4	Citric Acid(Anhydrous)	8	8	8	12	12	12	16	16	16
5	CMC	20	20	20	20	20	20	20	20	20
6	Sodium Alginate	10	10	10	10	10	10	10	10	10
7	Mag. stearate	7	7	7	7	7	7	7	7	7
8	Talc	5	5	5	5	5	5	5	5	5
9	MCC	65	40	15	61	36	11	57	32	7
Total weight (mg)		530	530	530	530	530	530	530	530	530

Full Factorial Design: [14]

A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of HPMC K100M (X_1) and amount of citric acid (X_2) were selected as independent variables. Floating lag time, % release at 6 hours (Q_6) and % drug release at 12 hours (Q_{12}) were selected as dependent variables.

A statistical model incorporating interactive and polynomial term was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2$$

Where Y is dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i(b_1, b_2, b_{12}, b_{11} and b_{22} is the estimated coefficient for the factor X_1).The main effect (X_1 and X_2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X_1X_2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term ($X_1^2$and X_2^2) are included to investigate nonlinearity.

Pre-Compression Evaluation: [15-19]

Angle of Repose:

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blends were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = \frac{h}{r}$$

Where, **h**= height of the powder cone**, r**= radius of the powder cone.

Table 2: Standard values of angle of repose

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very Poor

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. The accurately weighed amount of sample taken in a 25 ml measuring cylinder measured /recorded the volume of packing and tapped 100 times on a plane hard wooden surface and tapped volume of packing recorded and LBD and TBD calculated by the following formula:

Bulk density [BD] = Weight of powder / Bulk volume

Compressibility index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD ,TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's index} = \frac{TBD - LBD}{TBD} x100$$

Hausner's ratio (HR)

This was calculated as the ratio of tapped density to bulk density of the sample

$$HR = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post-Compression Evaluation Parameter of Gabapentin Floating Tablets

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a citizen electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

$$\text{Percentage Deviation PD} = \frac{\text{W avg} - \text{W initial}}{\text{W avg}} * 100$$

Where,

W_{avg} = average weight and

W initial =initial weight

Table 3: Standards for uniformity of weight as per USP

Sr. No.	Average weight of a tablet	Percentage deviation
1.	130 mg or less	10
2.	More than 130 mg and less than 324 mg	7.5
3.	324 mg or more	5

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using precision dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using vernier caliper. Five tablets were used and average value was calculated.

Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). 20 tablets were initially weighed and transferred into Friabilator. The Friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by the following formula,

$$\text{Percentage Friability} = \frac{W - W0}{W} \text{ X } 100$$

Where,

W_0= initially weight,

W= weight after friability.

Percentages Friability of tablets less than 1% are considered acceptable.

Uniformity of Drug content

Twenty tablets were weighed and powdered in a glass mortar. Quantity of powder equivalent to 50 mg of Gabapentin was accurately weighed and transferred in a 50 ml volumetric flask add final volume in volumetric flask up to 50 ml using pH 1.2 buffer. Pipette out 5 ml and diluted up to 50 ml with 0.1N HCl pH 1.2 and measure the absorbance of the resulting solution using UV Visible spectrophotometer at of λ-max 210 nm.

Buoyancy lag time determination and Total floating time

The floating behavior of the tablets was visually determined, in triplicate, according to the floating lag time method described by Rosa et al. The *in-vitro* buoyancy was determined by the Buoyancy lag time. The tablets were placed in a 250 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface for floating was determined as the Buoyancy lag time and further floating duration of all tablets was determined by visual observation.

Tablet swelling ability/Swelling index

The swelling behavior of the tablets was determined in triplicate, according to the method described by Dorozynski et al. Briefly, a tablet was weighed (W1) and placed in a glass beaker, containing 250 ml of 0.1N HCl, maintained in a water bath at 37 ± 0.5°C. At regular intervals, the tablets were removed & the excess surface liquid was carefully removed by a filter paper. The swollen tablet was then reweighed (W2). The swelling index [SI] was calculated using the formula-

$$SI = (W2-W1)*100 / W1$$

***In-Vitro* Drug Release Studies**

In-vitro drug release of the samples was carried out using type-II dissolution apparatus (Paddle type). The dissolution medium, 900mL of 0.1N HCl buffer was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and 50 rpm. Tablet was placed in each vessel and operated the apparatus at 50 rpm for 12h. Withdrawn 5mL of the sample solution from each vessel through 5mL syringes up to 12 hours and replaced with equal volume of fresh dissolution medium previously equilibrated to 37 ± 0.5°C. Each sample was filtered through 0.45µm filter and collected in separate vials. The samples were analyzed by UV-Spectroscopy at 210 nm. The percentage drug released at different time points were calculated using the calibration curve of the standard solution. The release data were analyzed as per Zero order, First order, Higuchi and Peppas equation models.

***In-vitro* drug release studies details:**

Apparatus used	:	USP Type-2 Model, Electrolab.
Dissolution medium	:	0.1N HCL
Dissolution medium volume	:	900 ml
Temperature	:	37±0.5°C
Speed of paddle	:	50 rpm
Sampling intervals	:	1 hr
Sample withdraw	:	5 ml

Absorbance measured : 210 nm.

Data Analysis:

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order, Higuchi matrix, Peppas and model using PSP-DISSO–V2 or M.S Excel office. Based on the R-value, the best-fit model was selected.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation,

$$Q_t = Q_o + K_o t$$

Where Q_t = amount of drug dissolved in time t,

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant.

First order kinetics:

To study the first order release rate kinetics, the release rate data were fitted to the following equation,

$$\text{Log } Q_t = \log Q_o + K_1 t/2.303$$

Where,

Q_t = the amount of drug released in time t,

Q_o = the initial amount of drug in the solution and

K_1 = the first order release constant.

Higuchi model (square root law):

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. And the equation is,

$$Q_t = K_H \cdot t^{1/2}$$

Where,

Q_t= amount of drug released in time t,

K_H = Higuchi dissolution constant.

Korsmeyer-Peppas release model:

To study this model the release rate data are fitted to the following equation,

$$Mt / M_\infty = K \cdot t^n$$

Where

Mt / M_{∞} = the fraction of drug release,

K = the release constant,

t = the release time and

n = the diffusion coefficient for the drug release that is dependent on the shape of the matrix.

Stability Studies:

The best formulation was subjected for one month stability study by exposing the tablets in their final packing mode to the temperature 40±2°C and relative humidity 75±5% in programmable environmental test chamber.

RESULTS AND DISCUSSION

Pre-formulation Studies:

Appearance:

White to off-white crystalline solid.

Solubility of Gabapentin:

Gabapentin is freely soluble in water, 0.1N HCl, 0.1N NaOH and in ethanol (95%); slightly soluble in chloroform. It is practically insoluble in ether.

Loss on Drying:

Loss on drying of Gabapentin was found to be 0.01 gm.

Determination of melting point:

The melting point of Gabapentin was found to be in the range of 163^{0}C.

U.V. Spectrum of Gabapentin:

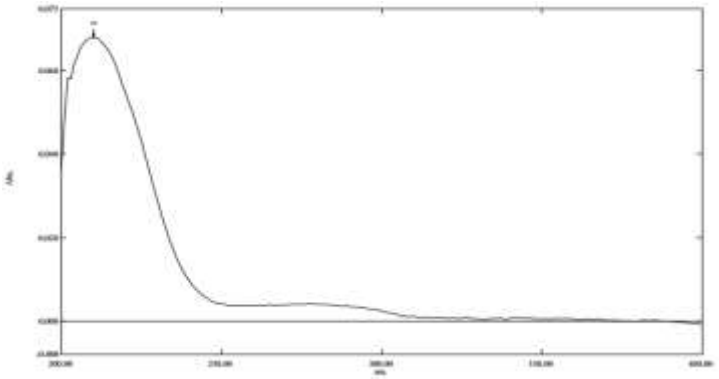

Figure 1: UV Spectrum of Gabapentin in 0.1N HCl (pH 1.2)

Table 4: Calibration Curve Values of Gabapentin in 0.1N HCl (pH 1.2)

Sr. No.	Concentration (µg/ml)	Absorbance at 210 nm)
1	00	0.000

2	05	0.142
3	10	0.271
4	15	0.432
5	20	0.572
6	25	0.731
7	30	0.830

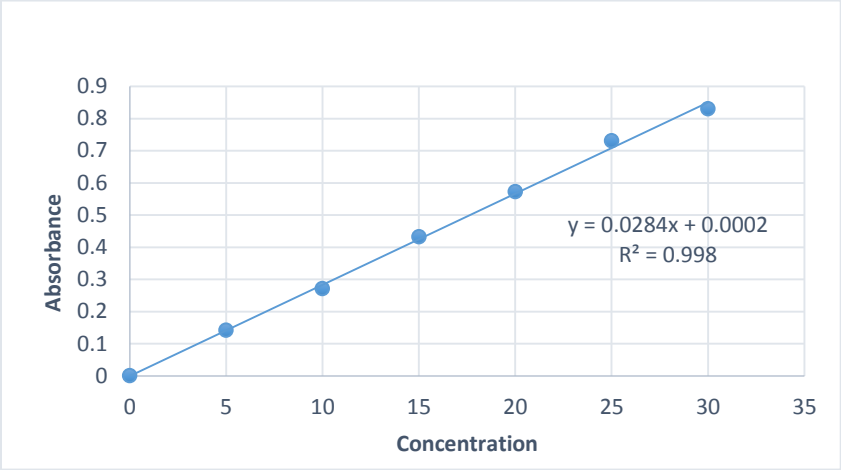

Figure 2: Standard curve of Gabapentin in 0.1N HCl P^H 1.2 at 210 nm

Compatibility study of Gabapentin and excipients:

Infrared spectroscopy is used to study the interaction of electromagnetic radiation with vibrational or rotational resonances within a molecular structure. The principal peaks depicted in Figure 6.3 for Gabapentin occur at wave numbers 700.77, 1292.07, 1389.43, 1464.46, 1608.27, 2854.06, 2919.83 and 3647.06. These peaks represents the various functional groups interpreted in table 2.

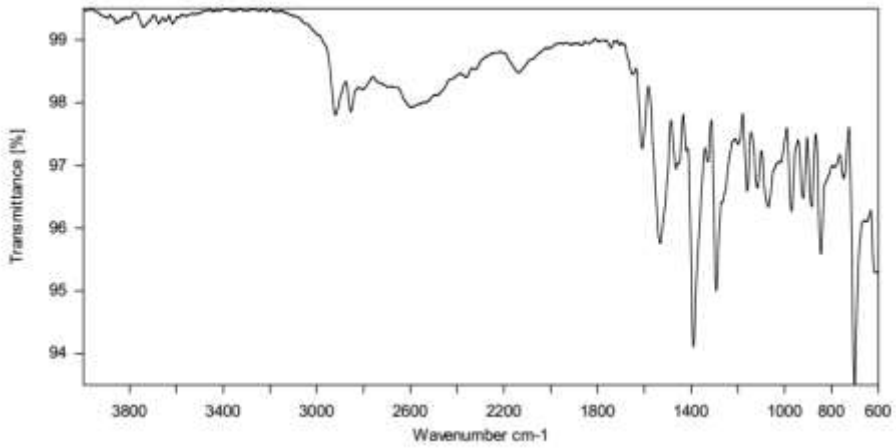

Figure 3: IR Spectra of Gabapentin

Table 5: Interpretation of IR Spectra:

Functional Group	Standard value	Obtained Value For API	Obtained value For GFT_7
Carboxylic Acid	1725-1700	1608.27	1693.54

C=O			
Carboxylic Acid O-H	3400-2400	2854.06	2848.42
Carboxylic Acid C-H	3000	2919.34	2914.84
Carboxylic Acid C-O	1320-1210	1292.07	1296.56
Primary Amine N-H	3500-3100	3647.06	3614.14
Primary Amine C-N	1350-1000	1389.73	1391.73
Cyclic $-CH_2-$	1465	1464.46	1693.54
Open Chain $-CH_2$	720	700.77	664.05

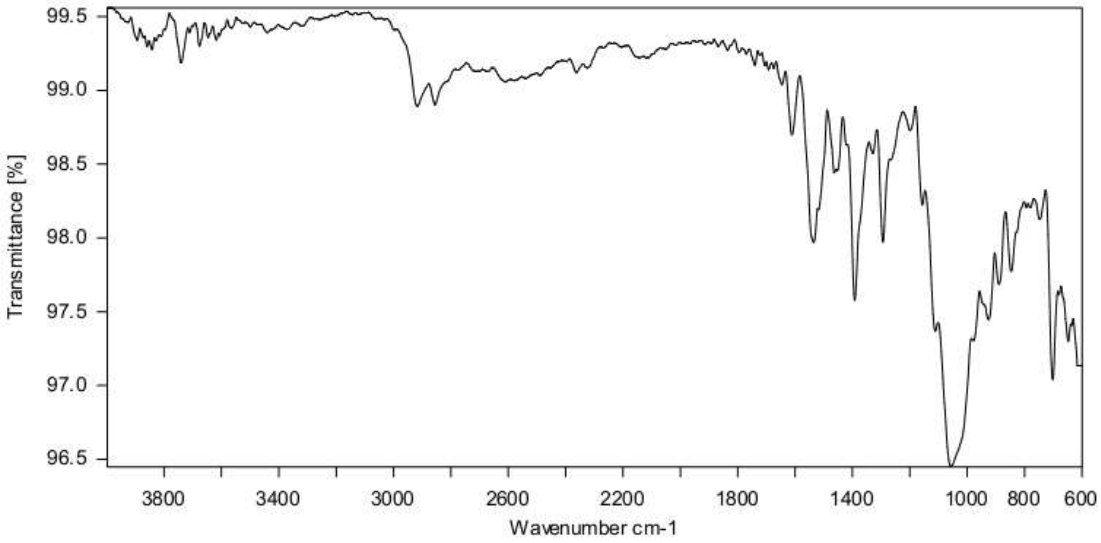

Figure 4: IR Spectra of Gabapentin and HPMC K100M

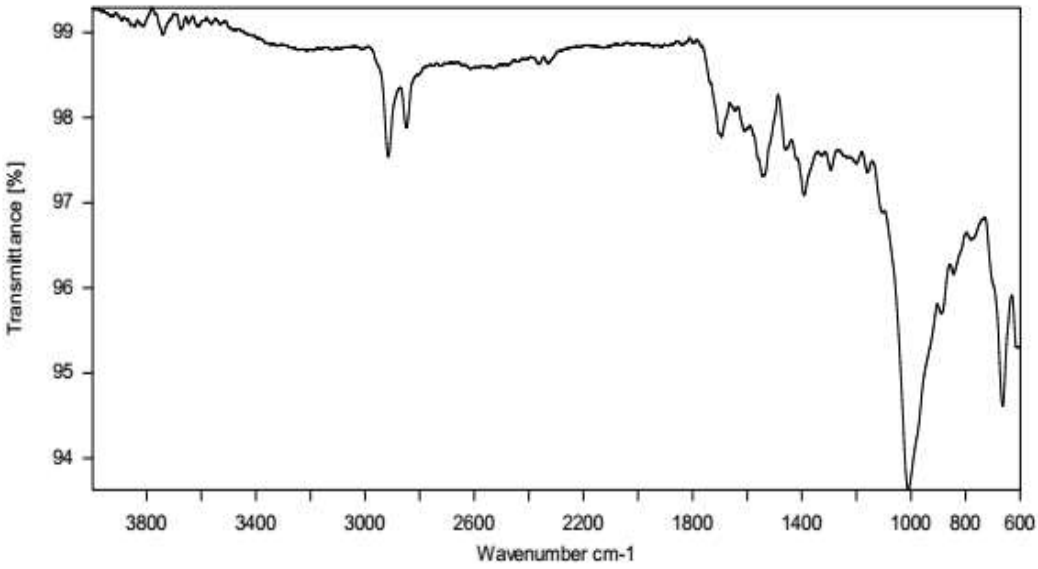

Figure 5: IR Spectra of optimized batch GFT_7

Full Factorial design:

Table 6: Formulation and dissolution characteristics of batches in 3^2 factorial designs

Batch code	Coded values		% drug release at 6 hr. (Q_6)	% drug release at 12 hr. (Q_{12})	Floating Lag Time (FLT)
	X_1	X_2			
GFT_1	-1	-1	59.17	95.15	10
GFT_2	0	-1	56.37	92.83	8
GFT_3	+1	-1	50.78	92.09	27
GFT_4	-1	0	57.76	97.47	7
GFT_5	0	0	62.51	94.20	70
GFT_6	+1	0	53.53	94.73	90
GFT_7	-1	+1	60.82	99.06	5
GFT_8	0	+1	64.08	95.89	98
GFT_9	+1	+1	58.76	94.94	92

Table 7: Translation of coded values to actual values

Coded Values	Actual values	
	X_1	X_2
-1	75	8
0	100	12
+1	125	16

Where X_1 - Amount of HPMC K100M, X_2 - Amount of Citric Acid, Q_6 - percentage drug release at 6 hours, Q_{12} - percentage drug release at 12 hours, and FLT (Floating Lag Time)

Table 8: Multiple Regressions output for Dependent variables.

Parameters	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Q_6	60.4022	2.6500	-2.4467	0.1566	-3.7033	1.4403	0.92156
Q_{12}	94.6700	1.6725	-1.6533	-0.4375	1.1950	-0.2150	0.97974
FLT	64.6333	21.6417	31.1667	-19.025	-13.4500	20.1500	0.93084

The responses of formulation prepared by 3^2 factorial designs are indicated in table 6. The data clearly indicate that the Q_6, Q_{12} and FLT are strongly dependent on the selected independent variables. The fitted equation relating the response Q_6, Q_{12} and FLT the transformed factors are shown in equation 6.1, 6.2 and 6.3 respectively.

$Q_6 = 60.4022 + 2.6500X_1 - 2.4467X_2 + 0.1566X_1^2 - 3.7033X_2^2 + 1.4403X_1X_2$. (Eq.6.1)

($R^2 = 0.92156$)

$Q_{12} = 94.6700+1.6725X_1-1.6533X_2- 0.4375X_1^2 + 1.1950X_2^2-0.2150X_1X_2$ ….. (Eq.6.2).

($R^2 = 0.97974$)FLT=$64.6333+21.6417X_1+31.1667X_2-19.0250X_1^2–13.4500X_2^2+20.1500X_1X_2$….

(Eq.6.3) ($R^2 = 0.93084$)

The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries, (i.e., positive or negative). Positive or negative signs before a coefficient in quadratic models indicate a synergistic effect or an antagonistic effect for the factor. The high values of correlation coefficient for Q_6 ($R^2 = 0.92156$), Q_{12} ($R^2 = 0.97974$), FLT ($R^2 = 0.93084$) indicate a good fit.

Equation 6.1 for Q_6 showed b_1, b_{11} and b_{12} positive but b_2 & b_{22} negative this reveals that negative value of b_2 decreases the effect with increasing the concentration of X_2 from -1 to +1. Percentage release at 6 hr. (Q_6) was found to be 57.76 to 60.82 for batches containing X_1 at -1 level, 50.78 to 58.76 for batches containing X_1 at +1 level, 56.37 to 62.51 for batches containing X_1 at 0 level.

Equation 6.2 for Q_{12} showed b_1 & b_{22} positive, but b_2, b_{11}& b_{12} negative this reveals that negative value of b_2 decreases the effect with increasing the concentration of X_2 from -1 to +1.Percentage release at 12 hr. (Q_{12}) was found to be 95.15 to 99.06 for batches containing X_1 at -1 level, 92.09 to 94.94 for batches containing X_1 at +1 level, 92.83 to 95.89 for batches containing X_1 at 0 level.

Equation 6.3 for FLT showed b_1, b_2 & b_{12} positive, but b_{11} & b_{22} negative this reveals that up to certain level increases in X_1^2 and X_2^2 from -1 to +1 increases FLT. Value of FLT was found to be 5 to 10 sec for batches containing X_1 at -1 level, 27 to 92 sec for batches containing X_2 at +1 level, 8 to 98 sec for batches containing X_2 at 0 level.

The main effects (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction terms (X_1, X_2, X_1X_2, X_1^2, $X_2^{2)}$ shows the response changes when two or more factors are simultaneously changed.

The equation for Q_6 (Eq. 6.1) suggest that the factor X_1 has more significant effect on drug release at Q_6, therefore high level of factor is not selected for increasing drug release. From equation 6.2 it can conclude that single factor X_2 not more effect on Q_{12}, but factor in combination X_1 and X_2 shows positive effect. It means that the when the value of X_1 increases Q_{12} decreases. From equation 6.3 positive sign of X_2 it concludes that FLT depends on value of X_2 but the magnitude of coefficient indicates that the factor X_1 has more favorable effect on the dependent variables.

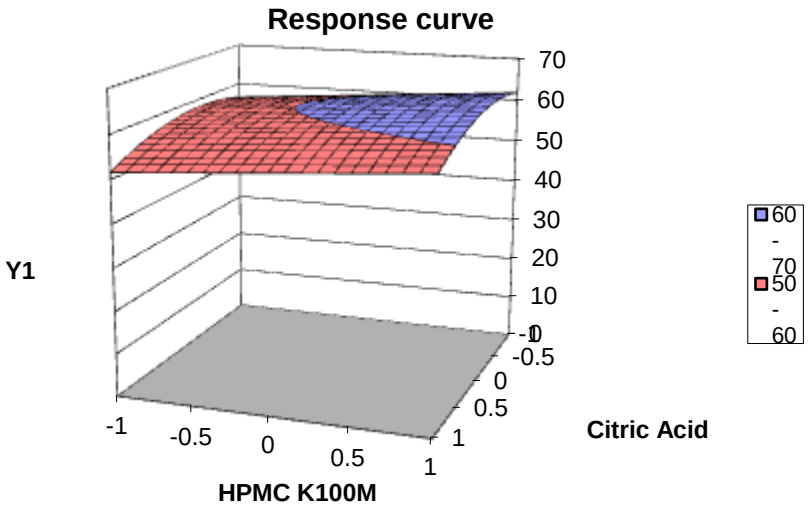

Figure 6: Response surface plot for Q_6

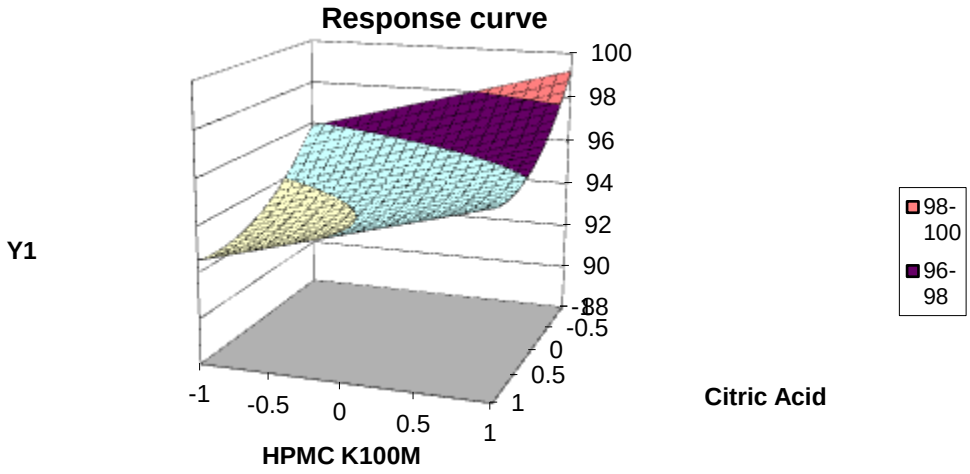

Figure 7: Response surface plot for Q_{12}

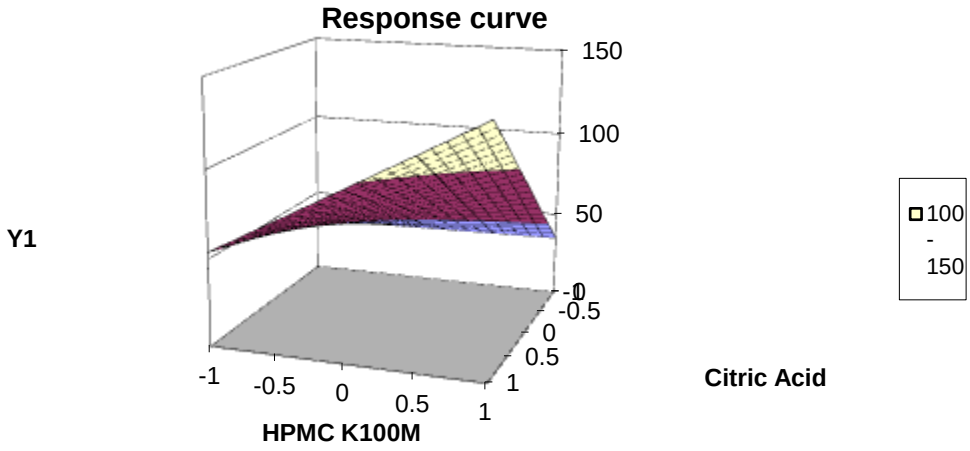

Figure 8: Response surface plot for FLT

Figure 6, 7 and 8 show the plot of the amount of HPMC K100M (X_1) and amount of citric acid (X_2) versus Q_6, Q_{12}, and FLT respectively. The statistical analysis of the factorial design batches

was performed by multiple linear regression analysis using Microsoft Excel. The plot was drawn using PCP-Disso V3 software, India. The data demonstrate that both X_1 and X_2 affect the drug release Q_6, Q_{12} and floating lag time. It may also be concluded that the low level of X_2 (amount of citric acid) and the higher level of X_1 (amount of HPMC K100M) favor the preparation of floating sustained release Gabapentin tablets. The high value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 has a significant effect on Q_{12}. It can be concluded that the drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. An increase in the concentration of citric acid (X_2) and amount of HPMC K100M (X_1), increase and decrease rate of release of floating Gabapentin tablet respectively.

Figure 6 shows the influence of content of HPMC K100M and citric acid on Q_6. It was found that percentage drug release increase with decrease in content of HPMC and citric acid. Although the content of HPMC and citric acid significant influence on the Q_6 it ranged from 50.78 to 64.08 from the graph it is observed that percentage drug release at 6 hr. (Q_6) is increases.

Figure 7 shows multiple regressions analysis for percentage drug release at 12 hr. (Q_{12}) showed the significant contribution of both the factors on response. Increasing the concentration of polymer (X_1) and citric acid (X_2) retardation of the drug release at Q_{12} is observed.

Figure 8 shows the influence of content of HPMC K100M and citric acid on FLT. The data clearly indicate that the values of FLT are strongly dependent on the independent variable

Pre-compression evaluation of powder blends:

Table 9:Pre-compression evaluation parameter

Batch Code.	Bulk Density(gm/ml)	Tapped Density (gm/ml)	Carr's index (%)	Hausner's Ratio	Angle of Repose(θ)
GFT_1	0.675±0.005	0.780±0.003	13.23±0.324	1.14±0.017	29.97±0.788
GFT_2	0.714±0.001	0.828±0.002	13.67±0.061	1.16±0.012	26.55±0.633
GFT_3	0.656±0.004	0.750±0.002	12.8±0.244	1.16±0.021	27.83±2.68
GFT_4	0.628±0.002	0.717±0.002	12.36±0.287	1.15±0.012	26.33±1.31
GFT_5	0.583±0.003	0.660±0.003	11.56±0.286	1.14±0.017	26.62±1.60
GFT_6	0.609±0.002	0.715±0.002	15.44±0.033	1.15±0.025	27.61±0.744
GFT_7	0.561±0.003	0.651±0.003	14.12±0.08	1.16±0.00	26.82±0.981
GFT_8	0.530±0.002	0.612±0.004	13.54±0.498	1.15±0.005	31.83±2.72
GFT_9	0.607±0.003	0.686±0.306	11.50±0.675	1.13±0.012	30.55±2.85

Post compression evaluation of Gabapentin tablets:

Table 10: Evaluation of Gabapentin floating tablets

Batch No.	Hardness Kg/cm^2	Thickness (mm)	Wt Variation of Tablet (mg)	Friability (% w/w)	Drug Content (%)
GFT_1	6.1±0.346	5.25±0.50	526±2.30	0.417	99.95
GFT_2	6.3±0.1	4.10±0.80	529±2.82	0.358	100.35

GFT_3	6.2±0.251	5.29±0.84	527±2.626	0.58	101.10
GFT_4	6.2±0.251	5.10±0.15	527±1.481	0.83	100.12
GFT_5	6.1±0.264	4.90±0.19	528±1.763	0.56	101.1
GFT_6	6.3 ± 0.416	5.4±0.50	532±2.424	0.82	99.0
GFT_7	6.7 ± 0.416	4.8±0.30	530±2.233	0.37	99.99
GFT_8	7.1 ± 0.36	4.9 ± 0.25	530±2.330	0.30	99.10
GFT_9	5.1 ± 0.13	5.5 ± 0.55	529±3.497	0.69	100.99

***In-vitro* buoyancy study of all batches:**

Table 11: FLT and TFT values of all batches

Batch Codes	Floating lag time (sec.)	Total floating time (hrs.)
GFT_1	10	>12
GFT_2	8	>12
GFT_3	27	>12
GFT_4	7	>12
GFT_5	70	>12
GFT_6	90	>12
GFT_7	5	>12
GFT_8	98	>12
GFT_9	92	>12

Swelling index:

Table 12: % swelling for all batches

Time (hrs.)	GFT_1	GFT_2	GFT_3	GFT_4	GFT_5	GFT_6	GFT_7	GFT_8	GFT_9
1	59.23	63.42	66.73	60.72	65.14	65.84	57.33	69.58	70.83
2	81.14	88	96.95	82.37	89.90	97.35	71.99	91.25	99.24
3	99.04	108.57	125.66	104.02	106.09	116.41	90.41	123.95	116.28
4	122.85	129.52	153.42	123.37	118.66	129.43	106.01	150.38	138.44
5	132.95	148.95	173	148.08	121.90	142.07	112.40	163.11	146.59
6	144.57	160.19	175.47	154.98	155.80	150.37	116.91	166.15	150
7	148.95	174.47	195.24	175.09	171.04	154.33	120.67	168.63	159.46
8	157.14	189.52	204.18	189.27	188.6	178.30	124.06	179.65	169.69

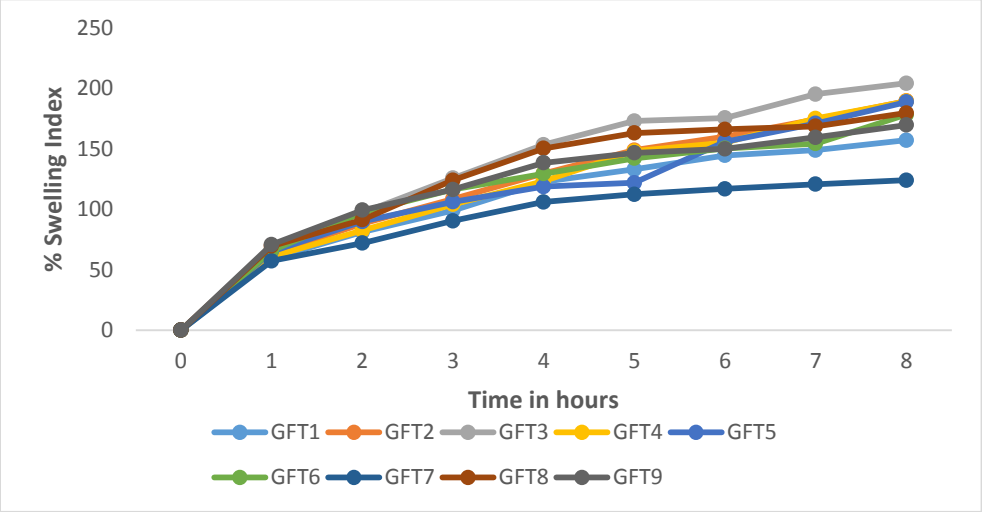

Figure 9: % Swelling Index of batches GFT_1-GFT_9

***In-vitro* drug release study:**

Table 13: Cumulative % Drug Release

Time (hrs.)	GFT_1	GFT_2	GFT_3	GFT_4	GFT_5	GFT_6	GFT_7	GFT_8	GFT_9
1	20.47	19.20	17.40	21.42	19.94	18.57	22.79	20.68	19.73
2	27.86	26.07	23.74	27.44	27.97	26.70	31.24	28.60	27.76
3	35.15	32.93	30.61	35.47	39.69	32.93	38.74	33.57	33.04
4	42.33	39.80	38	42.33	42.54	41.91	45.61	40.75	39.90
5	49.09	46.24	44.66	50.04	50.78	48.67	54.06	48.88	49.30
6	59.17	56.37	50.78	57.76	62.51	53.53	60.82	64.08	58.76
7	64.30	60.29	57.65	65.68	69.78	62.51	68.42	72.33	67.47
8	71.28	67.16	64.41	83.42	79.52	70.01	85.96	78.67	72.97
9	78.99	74.55	70.75	90.29	84.27	86.49	91.77	84.27	83.95
10	85.85	80.26	76.56	94.62	87.86	89.97	95.57	87.33	87.33
11	94.62	88.18	83.74	96.42	91.98	92.30	97.58	93.35	92.83
12	95.15	92.83	92.09	97.47	94.20	94.73	99.06	95.89	94.94

Data Analysis

***In-vitro* Drug Release Kinetic:**

Drug release data fitted into kinetic model including the zero order, First-order, Higuchi matrix, Korsmeyee-Peppas release equations to find the equation with the best fit.

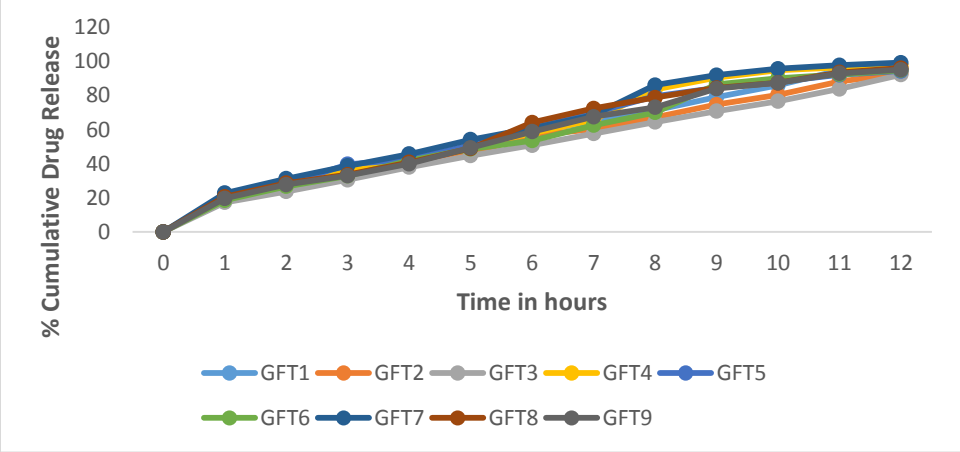

Figure 10: Comparative *In-vitro* Release Profile According to zero order kinetics for formulations GFT_1-GFT_9.

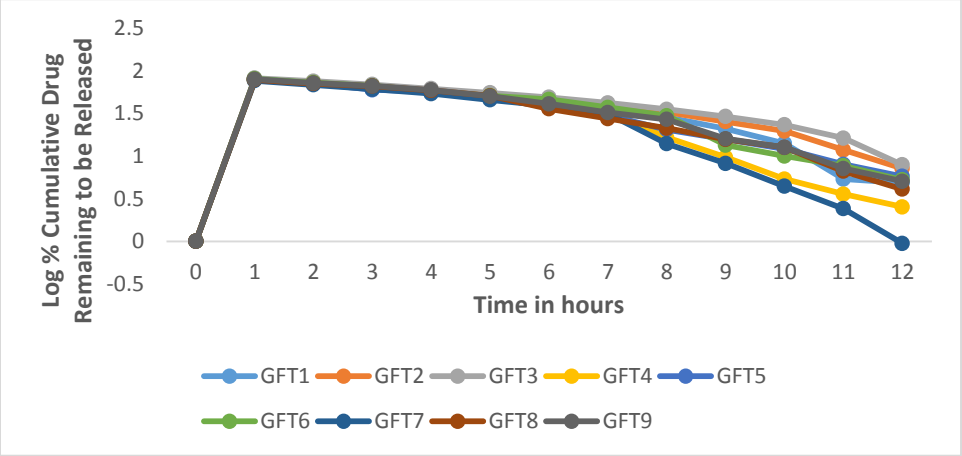

Figure 11: Comparative *In-vitro* Release Profile According to first order kinetics for formulations GFT_1-GFT_9.

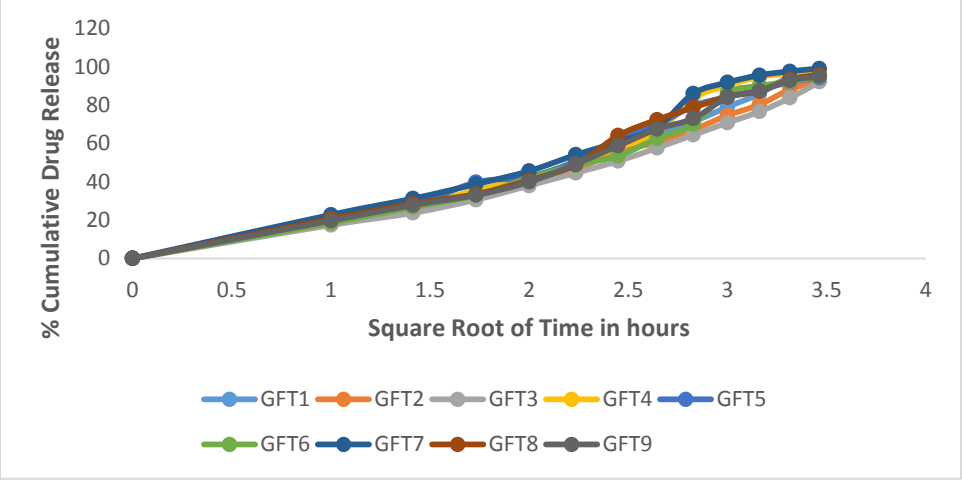

Figure 12: Comparative *In-vitro* Release Profile According to Higuchi matrix kinetics for formulations GFT_1- GFT_9.

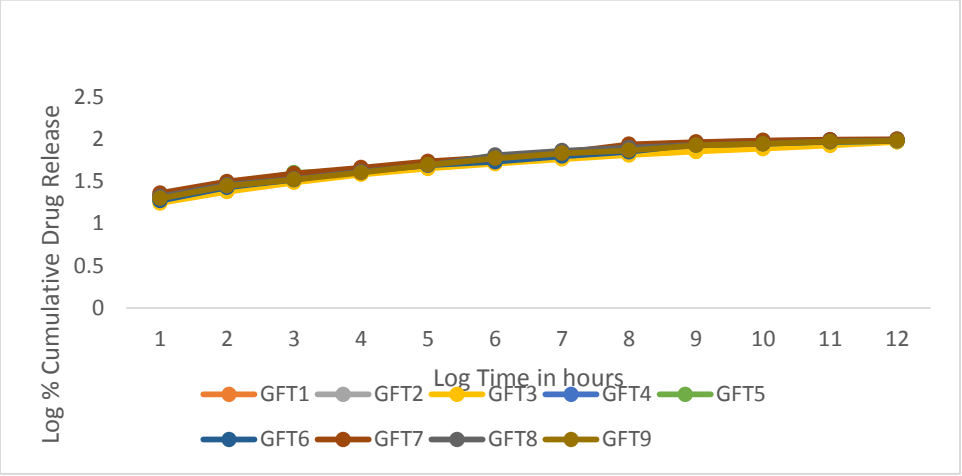

Figure 13: Comparative *In-vitro* Release Profile According to Korsmeyer-Peppas kinetics for formulations GFT_1-GFT_9.

***In-vitro* release kinetic parameters of floating tablets of Gabapentin are tabulated below.**

Table 14: Release kinetics for Korsmeyer- Peppas Model

Formulations	n	k	R^2
GFT_1	0.6176	0.0152	0.9333
GFT_2	0.6220	0.0144	0.9312
GFT_3	0.6483	0.0.0131	0.9257
GFT_4	0.6458	0.0154	0.9184
GFT_5	0.6286	0.0158	0.9506
GFT_6	0.6608	0.0141	0.9218
GFT_7	0.6089	0.0172	0.93
GFT_8	0.6365	0.0153	0.9371
GFT_9	0.6442	0.0147	0.9335

Table 15: Drug release kinetics of formulation (R^2-Value)

Batch Codes	Mathematical Models. (Kinetics)				
	Zero Order (R^2)	First Order (R^2)	Higuchi Matrix (R^2)	Korsmeyer-Peppas (R^2)	Best Fit Model
GFT_1	0.9833	0.0655	0.9694	0.9333	Zero Order
GFT_2	0.9862	0.0172	0.9678	0.9312	Zero Order
GFT_3	0.9905	0.0061	0.9607	0.9257	Zero Order
GFT_4	0.9715	0.1763	0.9506	0.9184	Zero Order
GFT_5	0.9664	0.0627	0.9751	0.9506	Higuchi Order
GFT_6	0.98	0.0705	0.953	0.9218	Zero Order
GFT_7	0.9565	0.2484	0.9638	0.93	Higuchi Order
GFT_8	0.9701	0.0856	0.9648	0.9371	Zero Order
GFT_9	0.9823	0.0672	0.9644	0.9335	Zero Order

Stability Study Data for % Drug Release:

Table 16: Stability study data

Condition	40^0±2C/75±5% RH	
Batch no.	GFT_7	
Test	Initial	1 month
Time (hrs.)	0	0
1	22.79	22.75
2	31.24	31.12
3	38.74	38.06
4	45.61	45.30
5	54.06	53.92
6	60.82	60.10
7	68.42	68.16
8	85.96	85.71
9	91.77	91.45
10	95.57	95.10
11	97.58	97.21
12	99.06	98.71

DISCUSSION:

Pre-formulation Studies:

Appearance: White to off-white crystalline solid of Gabapentin complies with USP.

Solubility of Gabapentin: Complies with USP and literature.

Loss on Drying: Complies with USP limit (less than 0.4).

Determination of melting point: The melting point of Gabapentin was determined by capillary tube method and it was found to be 163^0C which is same as that of literature value.

UV Spectrum of Gabapentin:

Pre-formulation studies were conducted prior to the development of sustained release tablets of Gabapentin. It was found that the estimation of Gabapentin by spectrometric method at 210 nm has good reproducibility. UV spectrum of Gabapentin shown in figure 1.

Standard Curve of Gabapentin:

The standard calibration curve Gabapentin was obtained by plotting absorbance vs. concentration. Table 4 shows the absorbance values of Gabapentin. The standard curve shown in figure 2. The standard calibration curve shows the correlation coefficient of 0.998. The curve was found to be linear in the concentration range of 5 to 25µg/ml (Beer's range) at 210 nm. The calculations of drug content, *in-vitro* drug release and stability studies are based on this calibration curve.

Drug-excipients Compatibility Studies:

FTIR Studies:

To study the compatibility of the drug with various polymers, IR spectra of drug and formulation components were carried out. The IR spectra of drug, drug-polymer and optimized formulation were shown in figures 3, 4 and 5. FTIR study was show no any major changes in peak absorbance indicates other excipients were compatible with Gabapentin (Table 5).

Formulation Design:

Formulation Design study is important for selection of appropriate excipients for preparation tablets. The three different concentrations of HPMC K100M and citric acid were used for trial preparation of tablets. The trial batches of tablets were prepared by direct compression method using other commonly used excipients. The composition of nine formulations is given in table 1.

Evaluation of Tablets:

Pre-compression evaluation parameters:

Bulk Density and Tapped Density:

The bulk density and tapped density of tablet blends of each batch was determined and was found in the range of 0.530±0.002 - 0.714±0.001gm/cm^3 and 0.612±0.004-0.828±0.002gm/cm^3 respectively indicates good flow. The results were shown in table 9.

Angle of repose (θ):

Table 3 shows the results obtained for angle of repose of all the formulations. The values were found to be in the range of 26.33^0±1.31 to 31.83^0±2.72. All formulations showed the angle of repose within 35^0. It indicates that all formulations showed good flow properties. The results were shown in table 9.

Carr's index (Compressibility index):

Compressibility index of tablet blend of each batch was determined and was found in the range of 11.50±0.675-15.44±0.033% indicating the powder blend have the required flow property for compression which is desirable for content uniformity and less weight variation in final tablets. The results were shown in table 9.

Hausner's ratio:

Hausner's ratio of the powder was determined from the loose bulk density and tapped bulk density. Hausner's ratio of all the formulations lies within the acceptable range. The Hausner's ratio of all the formulations is in the range of 1.13±0.012 to 1.16±0.021. It is shown in table 9.

Post-compression evaluation parameters:

All the formulations were subjected for organoleptic, physical and chemical evaluations. Shape, uniformity of thickness, hardness, friability, weight variation, drug content, *in-vitro* dissolution studies were carried out.

Size, shape and color of tablets:

Randomly picked up tablets from each formulation batch examined under lens for shape and in presence of light for color. The tablet shows circular, ovate shape and white in color. All ingredients used were white in color. There was no change in color and odor of the tablets in all the formulations. It indicates that all the excipients used were compatible with the drug and did not cause any chemical reaction that affects the properties of formulation.

Thickness:

The thickness of the tablets was measured by using Vernier caliper by taking the tablets randomly. The mean values are shown in table 10. The values are almost uniform in all formulations. Thickness was found in the range from 4.10±0.81 mm to 5.5±0.55 mm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches.

Hardness test:

The result of hardness is given in table 10. Hardness test was performed by Precision dial type hardness tester. Hardness was maintained to be within 5.1±0.13 kg/cm^{2}to 7.1±0.36 kg/cm^2. The

lower standard deviation values indicated that the hardness of all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.

Friability:

The result is given in table 10 was found well within the approved range (<1%) in all the formulation. Friability was in between 0.30% to 0.82% w/w. Results revealed that the tablets possess good mechanical strength.

Weight variation test:

All the tablets passed weight variation test as the % variation was within the pharmacopoeia limit of ±5 %. The weight of all the tablets was found to be uniform. This is due good flow property and compressibility of all the formulations. The result is given in table 10.

Drug content uniformity:

The content uniformity was performed for all seven formulations and results are shown in table 10. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 99 to 101.10 %w/w of Gabapentin. The results indicated that in all the formulations the drug content was uniform.

***In-vitro* buoyancy study:**

Buoyancy studies were performed using 0.1N HCl solution P^H 1.2 buffer at 37^0C (Table 11); the tablets floated and remained without disintegration. Floating Lag Time for all batches found in the range of 5 sec. to 98 sec. Total Floating Time for all batches was more than 12 hours shows good polymer integrity.

Swelling index:

Polymer matrices representing swellable matrix drug delivery systems are porous in nature. When these matrices come in contact with water or aqueous gastrointestinal fluid, the polymer absorbs the water and undergoes swelling or hydration. The rapid formation of a viscous gel layer upon hydration suggests that swelling is associated with polymer chain relaxation with volume expansion. The liquid diffuses through the polymer matrix at a constant velocity, and the rate of diffusion of the liquid and that of macromolecular relaxation of the polymer are almost of the same magnitude or, possibly, the rate of diffusion of the liquid is relatively higher than that of relaxation of the polymer segment.

This mechanism gives the idea regarding the water uptake study of various grades of polymer. This phenomenon is attributes to that the swelling is more due to water uptake and then gradually decreased due to erosion. Swelling measurement was performed separately in order to collect on

the basis of weight increase over time. The swelling is due to presence of hydrophilic polymer, which gets wetted and allows water uptake leads to increase in its weight.

Swelling studies were performed for all the formulations GFT_1-GFT_9 for 8 hours (Table 12) Swelling increases as the time passes because the polymer gradually absorbs water due to hydrophilicity of water (Figure 10)

***In-vitro* dissolution studies:**

All the nine formulations were subjected for the *in-vitro* dissolution studies using tablet dissolution tester (USP) TDT-08L, Electro lab. The samples were withdrawn at different time intervals, filter, diluted and analyzed at 210 nm. Cumulative drug release (mg) and Cumulative % drug release were calculated on the basis of mean amount of Gabapentin present in the respective tablet. The results obtained in the *in-vitro* drug release for formulations GFT_1 to GFT_9 are given in Table 13. The sustained drug release was observed in formulations GFT_1, GFT_2, GFT_3 releases 95.15%, 92.83%, 92.09% of drug respectively, at the end of 12 hrs. Formulations GFT_4, GFT_5 and GFT_6 which shows drug release 97.47%, 94.20%, 94.73% respectively at the end of 12 hrs. Formulations GFT_7, GFT_8, GFT_9 releases 99.06%, 95.89%, 94.94% respectively at the end of 12 hrs. This slow drug release of drug might be due to complex nature of polymer which having the net like structure with drug molecule. The drug release was completely achieved within 12 hrs. In all the formulations the drug release within 12 hrs.

In comparative study for the formulations GFT_7 drug releases 99.06%, at the end of 12 hrs and graphical representation was shown in figure 11.

Best optimized batch was GFT_7 because of highest percentage drug release at the end of 12 hrs among all the formulations and best fitted to Higuchi model.

***In-vitro* Drug Release Kinetics:**

The dissolution data was treated with different kinetic equations. The three parameters were used to study the release mechanism, n- Release exponent, k- Release rate constant and R- Correlation coefficient. Linear regression analysis & model fitting showed that as these formulation followed zero order, Higuchi-Matrix model, which has higher values of correlation coefficient. Thus, the release of is Gabapentin controlled by Higuchi-Matrix and Zero order mechanism.

$\text{Log } \% R = \log K + n \log t$

Where, % R is percentage drug release; K is release ratio constant and n-is the diffusion release exponent that could be used to characterize the different release mechanism. The value of exponent n can be used to characterize the release mechanism of controlled release matrix tablet. The mean diffusion exponent values (n) ranged from 0.6176 to 0.6483 indicating that diffusion

was the predominant mechanism of drug release from all these formulations indicating that the release mechanism was non-Fickian anomalous release. While the kinetic constant (k) ranged from 0.0131 to 0.0172. The optimized batch GFT_7 was show Higuchi-Matrix order model. (Table 14 and 15)

Stability study of batch GFT_7:

Stability is the essential factor for quality, efficacy and safety of drug product. The drug product with insufficient stability can result in change of their physical (hardness, dissolution rate, phase separation) as well as chemical characteristics (formation of high risk decomposition substance). Present study was carried out to check the dissolution behavior and physical appearance of optimized batch GFT_7. The batch GFT_7 was selected as an optimum batch and the stability study was carried out at accelerated conditions of 40^0C/75%RH condition for period of one month (Table 16). There was no any change in physical appearance in the dosage form of batch GFT_7 over a period of one month in accelerated condition (40^0±2/75±5%RH).

SUMMARY

Floating tablets have a bulk density less than gastric fluids and thus it remains buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system was floating on the gastric contents, the drug is released slowly at the desired rate from the system. Also floating tablets provide a constant and prolonged therapeutic effect which will reduce dosing frequency.

In the present study, Gabapentin floating tablets were prepared by using different ratio of hydroxypropylmethylcellulose K100M and citric acid. Gabapentin drug having physiochemical properties and short half-life make it suitable candidate for floating drug delivery system.

Initially, an extensive literature survey was done for the collection of theoretical and technical data. The review of literature, drug profile and excipient profiles, this was followed by procurement and characterization of raw materials used in the study.

The prepared floating tablets also characterized by FTIR spectroscopy to find out any chemical interaction between Gabapentin and polymer used. The prepared floating tablets were evaluated for bulk density, tapped density, Hausner's ratio, angle of repose, compressibility index, *in-vitro* buoyancy, *in-vitro* drug release study.

The results indicated that the significant effect was observed of increased polymer concentration, on said parameters in each case. Micromeritic study suggested good flow properties of powder blend prepared for tablets.

CONCLUSION

From the present study, the following conclusions were observed:

Gabapentin Floating Drug Delivery systems with shorter lag time can be prepared by direct compression method using HPMC K100M as a polymer and sodium bicarbonate and citric acid as gas generating agent.

- All the prepared tablet formulations were found to be good without capping and chipping.
- The present investigation described the influence of concentration of polymer (HPMC K100M), and citric acid on floating tablet of Gabapentin release using 3^2 full factorial designs.
- Result of multiple regression analysis indicated that both factors X_1, and X_2 significantly affect the FLT and percentage drug release at 6 (Q_6) and 12 (Q_{12}) hour and should be used to manufacture the tablet formulation with desired *in-vitro* dissolution.
- The *in-vitro* dissolution profiles of all the prepared Gabapentin Floating Drug Delivery system formulations were found to extend the drug release over a period of 10 to 12 hours and the drug release rate decreased with increase in polymer concentration.
- IR spectroscopic study indicates no drug-excipients interaction and physicochemical changes in the prepared formulations.
- Comparing the all formulations, GFDDS formulation of GFT_7 was considered as an ideal formulation which exhibited 99.06% of drug release in 12 hours, and floating lag time of 10 seconds with a total floating time of 12 hours.
- From the result it was observed that drug and polymer ratio influence the *in-vitro* drug release, and *in-vitro* buoyancy of Gabapentin floating tablets. Hence, the floating system of Gabapentin is expected to provide clinician with a new choice of safe and more bioavailable formulation in the management of GERD- Gastro-esophageal reflux disease. The study reveals satisfactory results with a further scope of pharmacokinetic and pharmacodynamics evaluation.

RECOMMENDATION

- The principle of floating drug delivery system can be adopted for other drugs acting locally in the stomach.
- The work can be extended to the *in-vivo* studies to conclude *in-vitro* and *in-vivo* correlation.
- Work can be extended to the *in-vivo* buoyancy studies in humans.

- The work can be carried out to study the effect of other response parameters like bio-adhesiveness etc., on floating and release rate of the drug.
- The work can be carried out to improve the physical stability of the dosage form like coating the tablet.

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REFERENCES

1. Vyas S.P., Roop K.K. Floating Drug Delivery Concepts and Advances. First Edition, New Delhi: 2002; 196-217.
2. Geetha, A., J. Kumar Rajendra, C.H. Krishna Mohan, V. Sateesh and P.N. Raju. A Review on Floating Drug Delivery Systems. Int J of Pharm Rese and Biomed Ana, 2012; 1(1): 1-13.
3. Mayavanshi AV, Gajar SS. Floating drug delivery system to increase gastric retention of drug: A Review. J. Pharm. Res., 2008; 1940: 345-348.
4. Vachhani savan R, Patel Dipen, Prajapati ST, Patel CN. J Chem. Pharma Res., 2010; 2(2): 57-64.
5. Gabapentin. The American Society of Health System Pharmacists. Retrieved Oct. 23, 2015.
6. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur. J. Neurol, 2010; 17(9): 1113–1118.
7. Chandra Kant Pandey et al. Preemptive use of Gabapentin significantly decreases post-operative & rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaes, 2004; 51(4): 358-363.
8. K. D. Tripathi. Essentials of Medical Pharmacology.5t^{h} Ed^{n}., New Jaypee Brothers, Delhi, 2003.
9. Goodman and Gilman. The Pharmacological Basis of Therapeutics. 11th Ed^{n}., McGraw-Hill, New York, 2006.
10. Venkata Srikanth Meka, Ambedkar Sunil Songa, Sreenivasa Rao Nali, Janaki Ram Battu, Venkata Ramana Murthy Kolapalli. Design and *In-vitro* evaluation of effervescent gastric floating drug delivery systems of propranolol HCl. Invest Clin. 2012; 53(1): 60-70.

11. CH.S warna Kamala Chinthala, K. Srinivas Reddy Kota, M. Hadassah, E. Hepsibha Metilda, S. Sridevi. Formulation and Evaluation of Gastroretentive Floating Tablets of Gabapentin Using Effervescent Technology. Int J Pharm Biomed Res. 2012; *3*(4): 202-208.
12. M. Vikramaditya Reddy, Ch. S. Vijayavani, V. Uma Maheshwara Rao. Formulation and Evaluation of Gabapentin Mucoadhesive Gastro Retentive Tablets. Int J Pharm Ana Res. 2013; 2(4): 151-163.
13. Anilkumar J. Shinde, Manojkumar S. Patil and Harinath N. More. Formulation and Evaluation of an Oral Floating Tablet of Cephalexin. Indian J Pharm Edu Res. 2010; 44(3).
14. Md. Sarfraz, B. Linga Reddy, H. Doddyya, Udupi Rajgopal H. Design and *In-vitro* Evaluation of Gastro Retentive Floating Tablets of Repaglinide. Int J Drug Dev and Res. 2013; 5(3): 322-332.
15. Hussain Mohammed Asif, Tadikonda Rama Rao, Maimuna Anjum. Design, Development and *In-Vitro* Evaluation of Intragastric Buoyant Tablets of Pioglitazone Hydrochloride. Int J Pharm Pharm Sci. 2014; 6(3): 91-96.
16. Muqtader Mohammed, Sadath Ali. Development and In-vitro evaluation of Gastro Retentive Floating Tablets of Famotidine. Int J Pharm & Ind Res. 2011; 1(4): 270-274.