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FLOATING GASTRORETENTIVE TABLETS FOR ANTICONVULSANT DRUGS: DEVELOPMENT AND EVALUATION

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Keywords:

Gastroretentive, Rabbit, Floating tablets, Gabapentin, *In vivo*

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ABSTRACT

Aim: Floating Gastroretentive Tablets for Anticonvulsant Drugs: Development and Evaluation. Method: Tablets were manufactured using the direct compression method, various assessment settings were used, and the following findings were obtained. Result and Conclusion: Factorial batches of floating gabapentin tablets revealed that the FFG2 batch had the longest buoyancy period (556 ± 5.23 s), the highest swelling index (103.46 percent), and the fastest drug release (99.75 percent) within 12 hours. The n value of FFG2 was discovered to be n = 0.9250, implying that FFG2 released in a non-Fickian or aberrant manner. The ANOVA analysis for the formulations revealed a probability value, i.e. a P-value less than 0.0500. The tablet properties did not alter significantly as a result of the stability tests. *In vivo* x-ray imaging studies clearly shown that the manufactured floating matrix tablets containing gabapentin stayed float in gastric fluid for up to 12 h in the upper part of the rabbit's small intestine, indicating that they had a good *in vivo* residence time.

INTRODUCTION

Recently, the gastrointestinal-retentive drug delivery system (GRDDS) has achieved enormous gain in the area of oral drug administration. It is possible to employ frequently for retaining the drug in the targeted area for sufficient time period and slowly releasing the medicine, which can deal with a number of issues associated with traditional oral administration, such as inadequate bioavailability. Among the numerous dosage forms created for human administration, oral formulations have received a significant amount of attention. In most cases, conventional oral administration systems have low bioavailability due to quick gastric emptying time, among other factors. However, recent technology advancements have resulted in various unique pharmaceutical devices mostly controlled release medication delivery systems, to address this issue. GRDDS is one such example, where a feature such as gastric hold on period combined with medication release for a longer period of time has considerably increased patient compliance. [1]

MATERIALS AND METHODS

Materials: Gabapentin was obtained as a gift sample from Alkem Laboratories, Mumbai. All other excipients were used of analytical grade.

Preparation of gastro-floating sustained-release tablets

A direct compression method was used to create floating tablet formulations containing 200 mg of gabapentin (GR). In brief, 200 mg of the medication, polymer, and other additives listed in Table1 were mixed in increments before being screened through a 40-mesh sieve (425 m). Magnesium stearate and refined talc were also included. A single-punch tablet compression machine (Cadmach, Ahmedabad, India) fitted with 10 mm concave-faced punches was used to compress powder mixes into tablets. The compression was adjusted to provide a tablet-crushing strength of 5 kg/cm2.

Table 1: Formulation composition of gabapentin floating tablet for preliminary batches

Sr. No	Name of Ingredients	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	FG9	FG10
1	Gabapentin	200	200	200	200	200	200	200	200	200	200
	Hydroxy ethyl cellulose (HEC)	90	100	110	120	130	140	150	160	170	180
2	Xanthan gum	30	30	30	30	30	30	30	30	30	30
3	Sodium bi-carbonate	35	35	35	35	35	35	35	35	35	35
4	Eudragit	154	144	134	124	114	104	94	84	74	64
5	Crosspovidone	20	20	20	20	20	20	20	20	20	20
6	Talk	3	3	3	3	3	3	3	3	3	3
7	Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Total		**535**	**535**	**535**	**535**	**535**	**535**	**535**	**535**	**535**	**535**

Experimental design

A 3^2 full factorial design was selected because an experiment may be designed to focus attention on a single independent variable. An alternative approach is to study the influence of one independent variable in conjunction with variations in one or more additional independent variables. The amount of hydroxy ethyl cellulose (HEC) (X1) and eudragit (X2) were selected as independent variables. Two-factor (X1, X2), three-level (-1, 0, +1) design can be developed. Two-factor were evaluated each at three-level and experimental trials were performed for all nine possible combinations.

The dependent variables were in-vitro drug release and floating lag time. Table 2 depicts the actual and coded formulation design of swellable gastro retentive tablets using a factorial design (3^2) configuration.

Table2: Formulation composition of factorial batches of gabapentin floating tablets

Sr. No	Name of Ingredients	FFG1	FFG2	FFG3	FFG4	FFG5	FFG6	FFG7	FFG8	FFG9
1	Gabapentin	200	200	200	200	200	200	200	200	200
2	Hydroxy ethyl cellulose (HEC)	53.33	106.66	160	160	106.66	160	53.33	53.33	106.66
3	Bagasse	30	30	30	30	30	30	30	30	30
4	Sodium bi-carbonate	35	35	35	35	35	35	35	35	35
5	Eudragit	42	84	42	126	126	84	126	84	42
6	Crosspovidone	20	20	20	20	20	20	20	20	20
7	Talk	3	3	3	3	3	3	3	3	3
8	Magnesium stearate	3	3	3	3	3	3	3	3	3
Total		**386.33**	**481.66**	**493**	**577**	**523.66**	**535**	**470.33**	**428.33**	**439.66**

***In-vitro* floating study (buoyancy study)** [2]

Each tablet or 10 mL raft system (put in a watch glass) was placed in a 250 mL beaker containing 200 mL of 0.1 N HCl (pH 1.2), and the system was kept at 37C0.5C in a water bath at 37C ±0.5C in a water bath. Their physical condition was monitored for 12 hours. The time between the introduction of the dosage form and its buoyancy on the 0.1 N HCl, as well as the time the dosage form remained floating (duration of floating), were recorded. For each formula, three replicate measurements were taken.

Swelling behavior [3, 4]

At 37°C, the GR tablets were immersed in 200 mL of 0.1 N hydrochloride with no rotation. The immersed tablets were withdrawn from the solution after 0.5, 1, 2, 4, 6, 8, and 12 hours and immediately wiped with a paper towel to eliminate surface droplets. The following calculation was used to calculate the percentage of swelling at each time point:

$$\%\text{swelling}= \frac{W2-W1}{W1}X100\frac{W2-W1}{W1}X100$$

Where, $W1$ is the initial weight of the tablet and $W2$ is the weight of the swollen tablets. The experiment was performed in triplicate.

***In- vitro* Dissolution Study**[5]

At a speed of 50 rpm, the tablet was placed in a dissolution test device USP II containing 900 ml of 0.1 N HCl. Every 1 hour for up to 12 hours, a 5 mL aliquot was removed and replaced with 5 mL of new dissolving medium. A double-beam UV spectrophotometer was used to evaluate each sample at 264.2 nm in comparison to a reagent blank. High performance liquid chromatography was used to determine the concentration of gabapentin in the sample.

Drug Release Mechanism[6]

The kinetics and mechanism of gabapentin release from tablet formulation were investigated using various kinetic models, including zero-order, first-order, Higuchi, and Hixon-Crowell. A graph was drawn between time and cumulative drug release for Zero-order. A graph between the log of cumulative drug release and time was plotted for First order. A graph was plotted in the Hixson-Crowell and Higuchi models, respectively,

between the cube root of the percentage remaining and time, and the cumulative drug release and the square root of time. The graph was used to compute the coefficient of determination (R2), and the highest value (1) was chosen as the best-fitting model.

Qt ¼ K0t

Where, K0 is the Zero-order rate constant and Qt is the amount of drug released from the tablet in time t.

$$\log Q = \log Q0 - \frac{K1t}{2.303} X100 \frac{K1t}{2.303} X100$$

Where, K1 is the First-order rate constant, Q is the remaining amount of drug in the tablet after time t, and Q0 is the initial amount of drug in the tablet.

$$Q0^{1-3} - Qt^{1-3} = _KHCt$$

Where, KHC is the Hixson-Crowell release constant. Q0 and Qt is the initial amount of drug in the tablet and the amount of drug released from the tablet in time t, respectively.

$$Qt = KH(t)^{1/2}$$

Where, KH is the Higuchi rate constant and Qt is the amount of drug released in time t.

Drug release from a polymeric matrix is best explained using the Korsmeyer-Peppas model and expressed as

$$\frac{Mt}{M\infty} = Kptn$$

Where, Mt/M1 is the fraction of drug release at time t, Kp is the Korsmeyer-Peppas constant and n is the release exponent. The value of n is calculated from the slope of a graph plotted between log Mt/M1 and log t. In case of cylindrical geometry (tablets), the drug release mechanism is considered Fickian, non-Fickian (anomalous transport), case II transport and super case II transport if n _ 0.45, 0.45 < n < 0.89, n = 0.89 and n > 0.89, respectively.

Stability Study [7]

According to ICH recommendations, gastroretentive tablets of GR optimised formulation were maintained in glass vials and subjected to 40 ^{0}C+ 20C/75 percent +5 percent RH for three months in the stability chamber.

***In vivo* Studies**

The protocol for the *in vivo* study was approved by the Institutional Animal Ethics Committee of Dr.Rajendra Gode College of Pharmacy in Malkapur and follows the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals, Ministry of Social Justice and Empowerment, Government of India. The final formulation floating tablet was studied *in vivo* using an X-ray imaging approach on the New Zealand albino rabbit. For the *in vivo* investigation, a floating tablet with an acceptable limit of barium sulphate was given to a rabbit, followed by 50 mL of water. The rabbit was placed in a supine position and an X-ray machine was used to check the position of the pill in the gastrointestinal region at predefined time intervals. During the experiment, the animals were fasted overnight with free access to water, and a radiograph was taken just before the floating pill was administered to check that there was no radio-opaque material in the stomach. The formulation was given to the animal via Pet Piller, followed by 50 mL of water. The radiographic imaging was performed in a supine position, and the distance between the X-ray sources and the animal was remained constant throughout the imaging, allowing the floating tablet movement to be easily observed. Gastric radiography was performed using an x-ray machine (WiproGEDX300 with the horizontal X-ray system, model SI01463128 capacity 300 MA100 KVP, Pune, India) at 0 h, 3 h, 6 h, 9 h, and 12 h and it was seen optimised dose form retained in rabbit stomach (12 h) and it was concluded that the prepared optimal dosage form was suitable for GRDDS. [8]

RESULT AND DISCUSSION

Post-Compression Parameters

Weight variation was found to be under the I.P limit of 5% in all prepared batches. The hardness ranged from 5.29 to 5.55 kg/cm2. All formulations had 1% friability, and the medication content was within the allowable range.

In-vitro Floating Study (Buoyancy Study)

All compressed tablets floated in vitro in a 100 mL beaker containing 0.1 N HCl, which was done in triplicate (pH 1.2). As demonstrated in Table 3, FG8 has a reasonable floating lag time (546 6.72 s) and total floating time (>12 h).

Table 3: ***In vitro* buoyancy and % swelling studies for gabapentin preliminary batches**

Formulation code	Floating lag time (s)	Total floating time (h)	% Swelling Index
FG1	135 ± 3.21	>12	120.56
FG2	495 ± 4.33	>12	146.17
FG3	435 ± 2.93	>12	158.69
FG4	489 ± 4.78	<12	180.37
FG5	490 ± 2.45	<12	196.26
FG6	502 ± 2.58	<12	218.69
FG7	490 ± 3.11	>12	229.91
FG8	546 ± 6.72	>12	257.38
FG9	521 ± 2.37	>12	267.66
FG10	479± 4.51	>12	294.58

Swelling Behavior

It was discovered that swelling increased with time because the polymer gradually absorbs water due to its hydrophilicity. In the current investigation, tablets of batch FG8 having a combination of HPMC K 15, Gaur gum, and Microcrystalline cellulose had a greater swelling index, and increasing the concentration of polymer resulted in a greater swelling index.

In vitro Dissolution Study

It was discovered that HEC and eudragit have a regulated influence on the drug release from the floating tablet of GR. The presence of varied concentrations of polymers HEC and eudragit caused differences in the drug release patterns of diverse formulations. Batch FG8 was deemed the best formulation since it demonstrated good buoyant qualities and regulated medication release for the targeted period of 12 hours. The optimised batch released 89.31% of the medication in 12 hours (Figure 1).

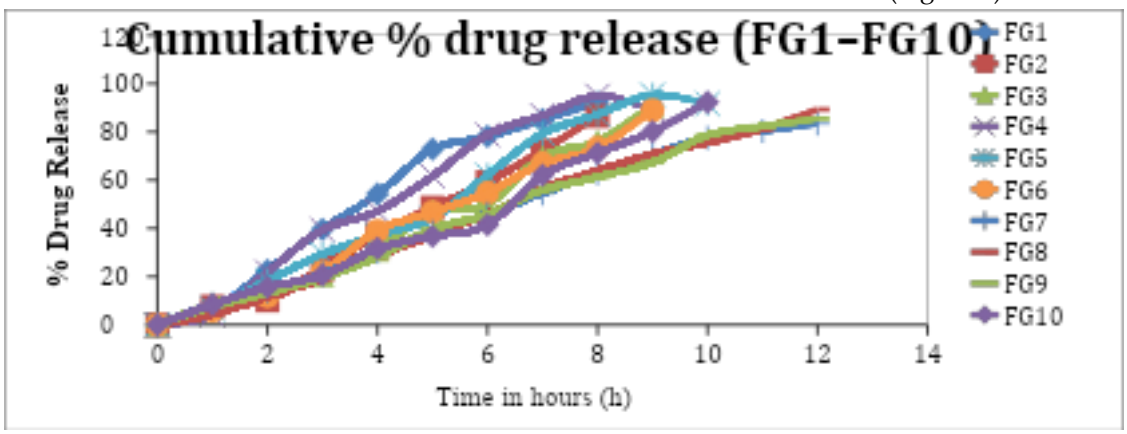

Figure 1: % Drug release for gabapentin preliminary batches

Because batch FG8 produced positive findings, it was decided to use this batch for 3^2 factorial designs.

Gabapentin Factorial Batches:

Floating Study (Buoyancy Study)

The buoyancy lag time ranged from 489 s (8.15 min) to 556 s for all formulations (9.26 min). The duration of buoyancy was proportional to the amount of CO_2 produced within the tablet. The FFG2 batch showed highest buoyancy time 556 ± 5.23 s (9.26 min).

Table 4: *In vitro* buoyancy and % swelling studies for gabapentin factorial batches

Formulation code	Floating lag time (s)	Total floating time (h)	% Swelling Index
FFG1	489 ± 2.31	>12	69.67
FFG2	556 ± 5.23	>12	103.46
FFG3	521 ± 4.63	>12	70.71
FFG4	534 ± 4.48	<12	72.96
FFG5	541 ± 3.45	<12	82.84
FFG6	519 ± 3.48	<12	100.34
FFG7	537 ± 4.21	>12	73.13
FFG8	541 ± 5.32	>12	79.20
FFG9	531 ± 4.27	>12	84.57

Swelling Behavior of GR Tablets

The tablets of batch FFG2 (103.46 percent) containing a combination of HEC, xanthan gum, and eudragit had the highest swelling index in the current investigation. The swelling index increased as polymer content rose. Hence, the viscosity of the polymer had a significant impact on the swelling process, matrix integrity, and floating capabilities.

Dissolution Study

Batch FFG2 was deemed the best formulation since it demonstrated good buoyant capabilities and regulated medication release for the targeted period of 12 hours. The improved formulation FFG2 demonstrated 99.75 percent drug release within 12 hours. (See Figure 2

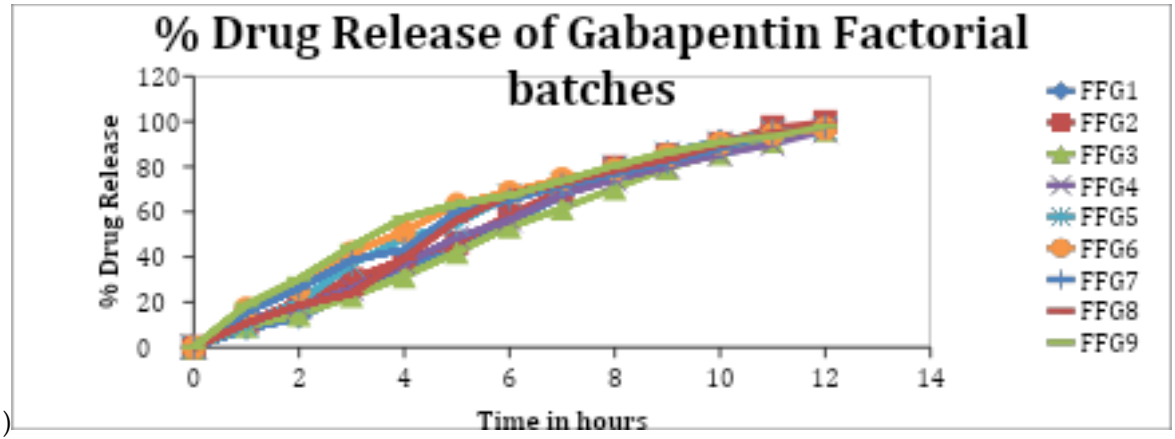

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Figure 2: % Drug release of gabapentin factorial batches

Drug Release Kinetics

The mechanism of release for the aforesaid formulations was found by calculating the R2 value for each kinetic model, namely zero-order, first-order, Higuchi, and Korsmeyer–Peppas, matching to each formulation's release data. The R2 value of the Korsmeyer–Peppas model was very close to one in most formulations, whereas

the R2 values of other kinetic models were not. Thus, it can be stated that the drug release follows the Korsmeyer–Peppas model mechanism, where R2 = 0.9983 of formulation FFG2 was determined to be the best among other formulations and n value was found to be n = 0.9250, implying that formulation FFG2 followed non-Fickian or anomalous release. The results are shown in Figure 3.

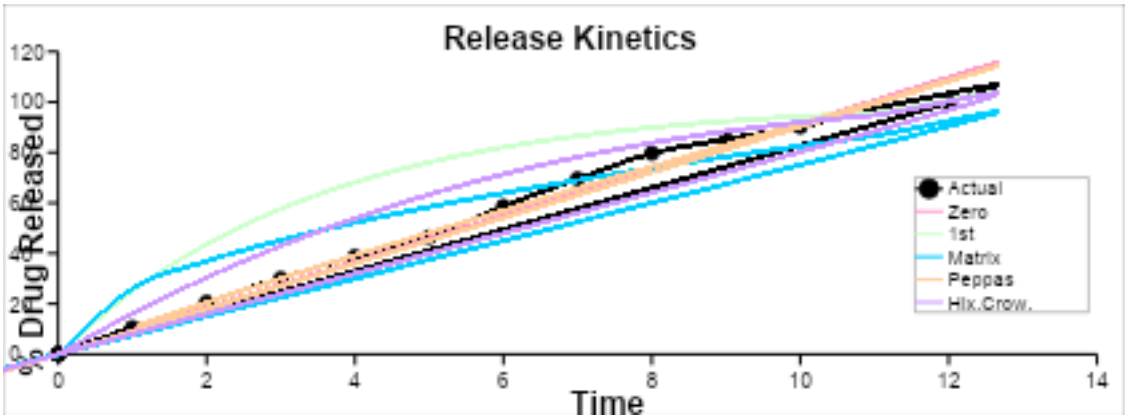

Figure 3: % release (average) with model fitting.

ANOVA

Anova Analysis for Drug Release and Floating Lag Time

The evaluation and interpretation of study findings are critical, and the p-value plays a crucial role in these findings. ANOVA was performed on the dependent variables drug release and floating lag time. The X1 and X2 coefficients were determined to be significant at p0.05, confirming that both variables have a substantial effect on the selected replies. Overall, both variables had a considerable impact on the responses. Design Expert Software Version 13, Stat-Ease, Inc. was used for ANOVA and response surface analysis.

Response Surface Analysis

The Quadratic Model from the regression analysis was used to create 3-D graphs in which the answers were represented by a curvature surface as a function of independent variables. The response surface plots shown in Figures 4 and 5 can be used to immediately visualize the relationship between the response and the independent variables. To analyze the evolution of the response surface, three-dimensional (3-D) surface plots for the obtained responses were created based on the model polynomial functions. These plots describe the relationship between the dependent and independent variables, or the impacts of two variables on the response at the same time. The response surface analysis for drug release and floating lag time was performed, and the results were noteworthy. Model F-values of 625.96 and 124.72 for drug release and floating lag time, respectively, indicate that the model was significant. Model terms are significant when the value of "P" is less than 0.0500.

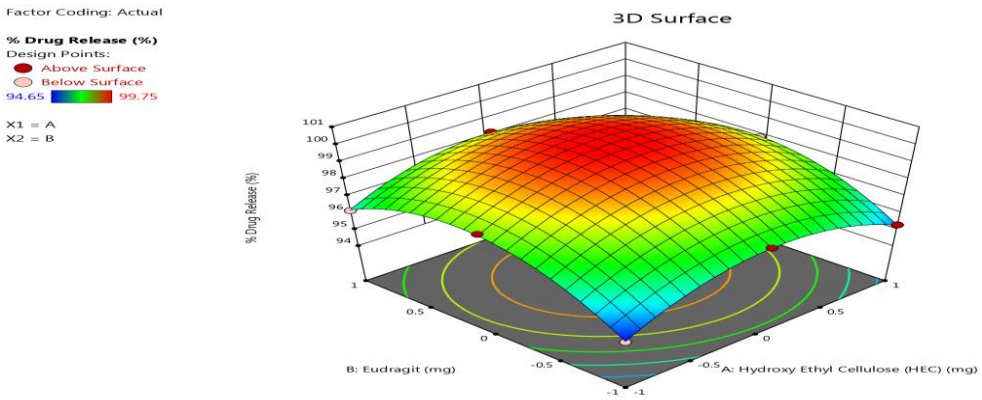

Figure 4: 3D graph of % drug release

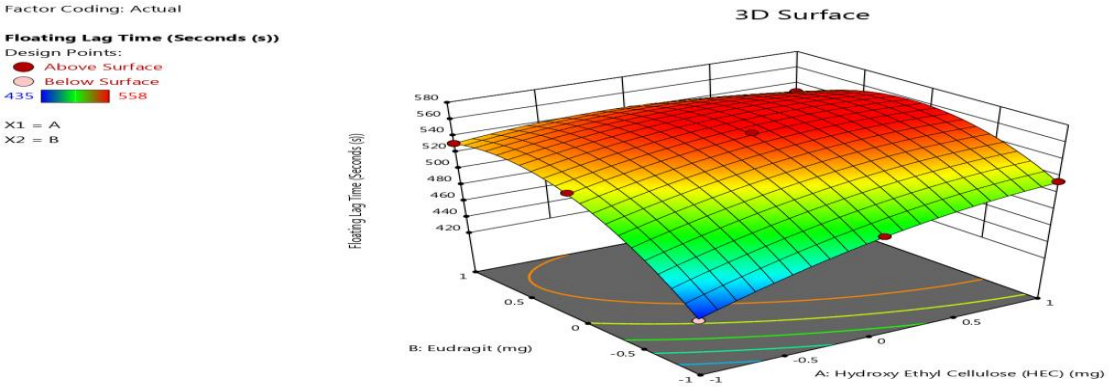

Figure 5: 3D graph of floating lag time

The "Pred R-Squared" of 0.9892 for drug release and 0.9483 for floating lag time agreed with the "Adj R-Squared" of 0.9974 for drug release and 0.9872 for floating lag time. A signal of appropriate quality is indicated by a ratio of 77.9742 for drug release and 35.0398 for floating lag time. The discovered probablity value, i.e. P-value, was also smaller than 0.0500. This model can be used to develop the design. The values are shown in Table 5and 6.

Response:-**DISSOLUTION AND FLOATING LAG TIME**

ANOVA for Response Surface Quadratic Model drug release

ANOVA for Quadratic model

Response 1: % Drug Release

Table 5: Analysis of variance table for dissolution (Partial sum of squares - Type III)

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	**Observation**
Model	20.05	5	4.01	625.96	0.0001	significant
A-Hydroxy Ethyl Cellulose (HEC)	0.0963	1	0.0963	15.03	0.0304	significant
B-Eudragit	2.18	1	2.18	340.92	0.0003	significant
AB	0.1190	1	0.1190	18.58	0.0230	significant
A^2	7.74	1	7.74	1207.46	< 0.0001	significant
B^2	9.92	1	9.92	1547.82	< 0.0001	significant
Residual	0.0192	3	0.0064			
Cor Total	20.07	8				

P-values less than 0.0500 indicate model terms are significant

ANOVA for Response Surface Quadratic Model Floating Lag time

Response 2: Floating Lag Time

Table 6: Analysis of variance table for floating lag time [Partial sum of squares – Type III]

Source	Sum of Squares	df	Mean Square	F-value	p-value	Observation
Model	11433.0	5	2286.6	124.72	0.0011	Significant
A-Hydroxy Ethyl Cellulose (HEC)	1944.00	1	1944.0	106.04	0.0020	Significant
B-Eudragit	4374.00	1	4374.00	238.58	0.0006	Significant
AB	1681.00	1	1681.0	91.69	0.0024	Significant
A^2	392.00	1	392.0	21.38	0.0190	Significant
B^2	3042.00	1	3042.00	165.93	0.0010	Significant
Residual	55.00	3	18.33			
Cor Total	11488.0	8				

***In-vivo* Study**

The batch FFG 2 was chosen for an *in vivo* x-ray imaging investigation in rabbits to determine product performance (residence time in stomach). Figure 6 shows photomicrographs recorded immediately after 0, 3, 6, 9, and 12 hours. The existence of a tablet in the upper small intestine was clearly observed, and it remains in the stomach, unaffected by drug release in rabbits. *In vivo* x-ray imaging studies clearly shown that the manufactured floating matrix tablets containing gabapentin stayed float in gastric fluid for up to 12 h in the upper part of the rabbit's small intestine, indicating that they had an excellent *in vivo* residence time in the rabbit's stomach. Photomicrographs was taken immediately after administration of the tablets with BaSo4 tracer and revealed the nature and position of the microspheres up to 12 h in the upper small intestine of rabbit.

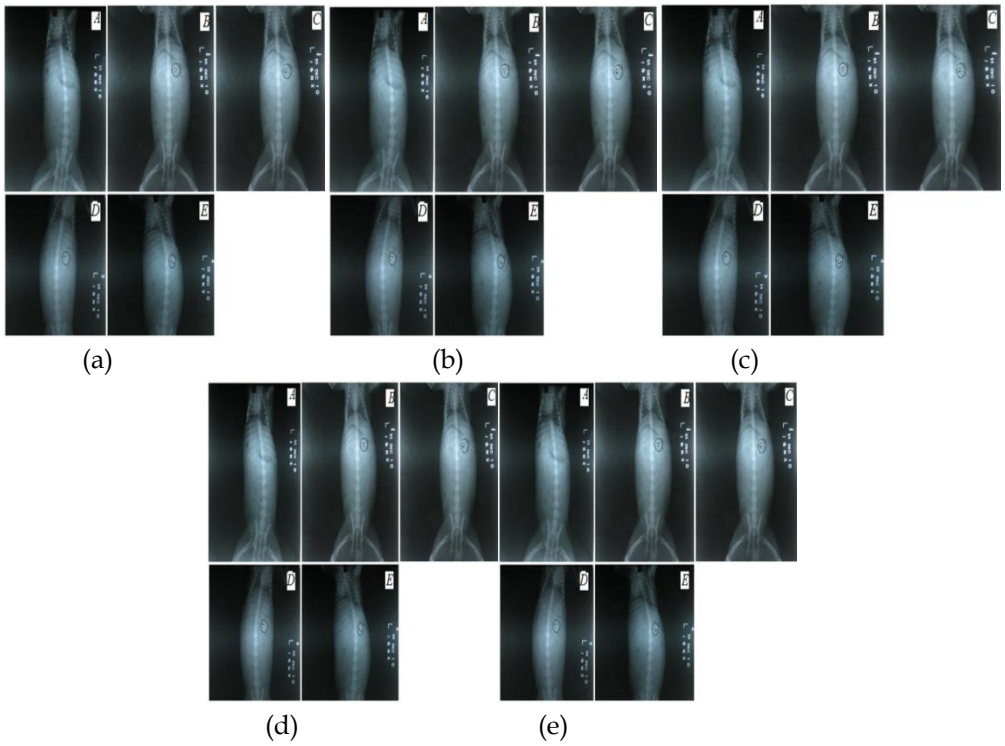

Figure 6: *In vivo* gastric retention of Gabapentin floating tablet in rabbit for 12 hours (a) for 0 hrs (b) for 3hrs (c) for 6 hrs (d) for 9 hrs (e) for 12 hrs.

Conclusion

Anticonvulsant medicines for gabapentin were created as floating gastroretentive pills. FG 8 was chosen for further research after showing good results for all evaluation parameters in the pilot batches. The factorial study results for batch FFG2 revealed the maximum buoyancy time 556 5.23 s (9.26 min), swelling index (103.46 percent), and medication release of 99.75 percent during 12 hours. FFG2 was found to be the best among the other formulations, and the n value was discovered to be n = 0.9250, implying that batch FFG2 followed a non-Fickian or anomalous release. The P-value found in an ANNOVA study for floating lag time and percent drug release was also less than 0.0500.

In terms of floating lag time, swelling index, and percent drug release, the stability analysis revealed no major changes in tablet features. *In vivo* x-ray imaging studies clearly shown that the manufactured floating matrix tablets containing gabapentin stayed float in gastric fluid for up to 12 h in the upper part of the rabbit's small intestine, indicating that they had an excellent *in vivo* residence time in the rabbit's stomach.

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