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DRUG DELIVERY SYSTEM FOR ANTICONVULSANT DRUG IN A FLOATING GASTRORETENTIVE ENVIRONMENT

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ABSTRACT

Objective: The present research was undertaken for the development and evaluation of floating gastroretentive tablets of anticonvulsant drug gabapentin.

Method: The gastroretentive tablets were made utilizing the direct compression approach. 32 factorial designs. The tablets were evaluated for different pre-compression and post-compression parameters. Besides, drug-polymer interaction was determined infrared spectroscopy using the Fourier transform and differential scanning colorimetry study. Finally, tablets were subjected to in-vivo study.

Result: The results revealed that among factorial batches of floating gabapentin tablets FFG2 batch possessed longest buoyancy period (556 ± 5.23 s), the highest swelling index (103.46 percent), and the fastest drug release (99.75 %) within 12 hours. The n value of FFG2 batch was n=0.9250, indicating taht FFG2 released in a non-Fickian or aberrant manner. The ANOVA analysis for the formulations showed P-value less than 0.0500. The stability study indicates floating tablets were persistent as evident from unchanged tablet properties. The results of in vivo x-ray imaging experiments are showed that the Gabapentin-containing floating matrix tablets float in gastric fluid for up to 12 hours in the upper part of the rabbit's small intestine. As a result, tablets had long in vivo residence duration.

Conclusion: The gastroretentive tablets prepared by 3^2 factorial designs could be beneficial and effective drug delivery strategy for the anticonvulsant drug gabapentin.

Keywords: Gastroretentive, rabbit, floating tablets, gabapentin, FTIR, sustained

INTRODUCTION

Recently; the gastrointestinal-retentive drug delivery system (GRDDS) made significant progress in oral drug administration. It is feasible to use it repeatedly for holding the drug in the targeted location for an extended period of time and slowly releasing the medicine, which can address various concerns connected with traditional oral delivery, such as insufficient bioavailability. However, recent technology advancements have resulted in various unique pharmaceutical devices mostly controlled release medication delivery systems, to address this issue. GRDDS is an example of how a feature like gastric hold on period paired with drug release over a longer period has significantly boosted patient compliance **[1]**. Although anticonvulsant drugs are typically used to treat epilepsy, they may also be used to treat neuropathic pain, bipolar mood disorder, and migraine prevention. There is some evidence that starting some anticonvulsants after a single seizure improves long-term prognosis but does not reduce the risk of damage or mortality **[2]**. Yadav and colleagues previously described and demonstrated that medications with difficulties such as an absorption window in the stomach or upper part of the duodenum, instability in alkaline pH, and a short half-life are more therapeutically efficacious due to longer retention time in the stomach **[2, 3]**.

METHOD AND MATERIAL

Gabapentin was provided as a free sample by Alkem Laboratories in Mumbai. All of the other excipients were of analytical grade.

Drug excipients compatibility study

FTIR study

The interaction between pure drug and different excipients used for the preparation of tablets was studied using FTIR. FTIR spectra (Shimadzu Corporation (Koyto, Japan) was recorded between 4000 cm-1 to 400 cm-1 **[4]**.

Differential Scanning Calorimeter (DSC)

Pure components, physical mixtures, and formulations were investigated using a TA Instruments DSC equipped with TRIOS software. Except for the pure API, all samples were stabilized by adjusting at 10 °C, then warming from 10 °C to 100 °C at a ramp timing of 10 °C/min with an active nitrogen cell purge flow of 50 mL/min. Pure API was equilibrated at 20 °C before being heated at a ramp rate of 20 °C/min from 20 °C to 150 °C **[5]**.

Preparation of gastroretentive sustained release tablets using 3^2 factorial designs

A direct compression method was employed to produce floating tablet formulations containing 200 mg of gabapentin (GR). In brief, 200 mg increments of the medication, polymer, and additives described in **Table 1** were combined before being screened via a 40-mesh sieve (425 m). There was also magnesium stearate and refined talc. Single-punch tablet compression machine (Cadmach, Ahmadabad, India) Powder mixtures were compressed into tablets using punches with 10 mm concave faces. The compression was tweaked to achieve a tablet-crushing strength of 5 kg/cm2. **Table 1** shows the tablet's composition.

Table 1: Composition of factorial design formulations

Ingredients	FG1	FG2	FG3	FG4	FG5	FG6	FG7	FG8	FG9
Gabapentin	200	200	200	200	200	200	200	200	200
Hydroxy ethyl cellulose (HEC)	53.33	106.66	160	160	106.66	160	53.33	53.33	106.66
Xanthan gum	30	30	30	30	30	30	30	30	30
Sodium bicarbonate	35	35	35	35	35	35	35	35	35
Eudragit	42	84	42	126	126	84	126	84	42
Crosspovidone	20	20	20	20	20	20	20	20	20
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Dicalcium phosphate	190.67	95.34	84	0	53.34	42	106.67	148.67	137.34
Total	577	577	577	577	577	577	577	577	577

Evaluation of designed formulations

Pre-compression Parameters

Bulk density and Tapped density

A 25ml measuring cylinder was filled with correctly metered powder from each formula that had been agitated to break any agglomerates that had formed. Following the measurement of the initial volume, the cylinder was allowed to fall under its own weight at 2 second intervals from a height of 2.5 cm onto a hard surface. The recording was kept going until there was no more change in volume **[6]**.

Hausner ratio

The Hausner ratio was determined by the following equation

Hausner's ratio=Tapped density/Bulk density

Angle of repose

The flow of the powder sample was measured by assessing the angle of repose using the funnel method. The angle of repose was calculated by the following equation

$\theta = \text{Tan}^{-1}(h/r)$

Post Compression Evaluation of Floating Tablets

Weight Variation

Ten tablets were selected randomly and weighed individually. The average weight was calculated and compared with individual tablet weight. The deviation in the average tablet weight should be within ±5%.

Hardness

Hardness of the tablets was determined using a Monsanto hardness tester. Ten tablets were randomly picked from each batch and analyzed for hardness.

Friability

The friability of core tablets was determined using Roche Friabilator. Pre-weighed tablets were transferred into friabilator and operated at 25 rpm for 4minutes. The tablets were measured again (Final) and %friability was calculated. Friability of tablets less than 1% are considered acceptable.

$$\mathbf{F} = \frac{\textbf{Initial weight} - \textbf{final weight}}{\textbf{Initial weight}} \times \mathbf{100}$$

Drug Content

Ten tablets were weighed and crushed into a fine powder in a mortar. A piece of the powder weighing 100 mg of gabapentin was carefully weighed and put to a 100-ml volumetric flask containing methanol. It was physically shaken for 1 hour and filtered via Whatman filter paper. An UV spectrophotometer was used to test absorbance against a blank at 264.2 nm after appropriate dilution. If the tablet amount falls between 90 and 110 percent, the drug content of the floating tablets matches the standards **[3, 7]**.

In-vitro floating study (buoyancy study)

Each pill or 10 mL raft system (placed in a watch glass) was put in a 250 mL beaker containing 200 mL of 0.1 N HCl (pH 1.2), and the system was held in a water bath at 370.5 oC. The time between the introduction of a 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 **[8]**.

Swelling behavior

The produced tablets were immersed in 200 mL of 0.1 N hydrochloride without rotation for 0.5, 1, 2, 4, 6, 8, and 12 hours before being withdrawn from the solution. Surface droplets were quickly removed by wiping the tablets with a paper towel. The proportion of swelling at each time point was calculated using the equation below.

$$\%\ \textbf{swelling} = \frac{\mathbf{W2} - \mathbf{W1}}{\mathbf{W1}} \times \mathbf{100}$$

Where, *W*1 is the initial weight of the tablet and *W*2 is the weight of the swollen tablets **[9, 10]**.

In-vitro dissolution study

The dissolution test was conducted using USP type-II apparatus in 900 ml of 0.1 N HCl at 50 RPM and 37±0.5 ºC temperature. The 5 mL aliquot was removed after 1 hr and replaced with 5 mL of new dissolution medium for 12 hrs. The samples were filtered, diluted appropriately, and the drug concentration was measured using a UV spectrophotometer set to 264.2 nm **[11]**.

Drug Release Mechanism

Mechanism of Drug Release Various kinetic models, including zero-order, first-order, Higuchi, and Hixon-Crowell, as well as the Korsmeyer-Peppas model, were used to explore the kinetics and mechanism of gabapentin release from tablet formulation. The coefficient of correlation (R^2) was determined and the highest value was chosen as the best-fitting model **[12]**.

Stability Study

The study was conducted according to ICH guidelines. The gastroretentive tablets of optimized formulation in glass vials subjected to 40±20 ºC and 75 %±5 % RH for three months in the stability chamber and evaluated for different parameters **[13]**.

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. On the New Zealand albino rabbit, the final formulation floating tablet was studied in vivo using an X-ray imaging method. A rabbit was given a floating tablet with an adequate amount of barium sulphate, followed by 50 mL of water. An X-ray machine was used to check the position of the pill in the gastrointestinal region at predetermined time intervals while the rabbit was in a supine position. The animals were fasted overnight and given free access to water during the experiment, and a radiograph was obtained just before the floating pill was given to ensure that there was no radio-opaque material in the stomach. The animal received the formulation via Pet Piller, followed by 50 mL of water. The radiographic imaging was done in a supine position, with the distance between the X-ray sources and the animal being constant throughout the imaging, allowing for easy observation of the floating tablet movement. At 0 h, 3 h, 6 h, 9 h, and 12 h, gastric radiography was completed using an x-ray machine (WiproGEDX300 with the horizontal X-ray system, model SI01463128 capacity 300 MA100 KVP, Pune, India) **[14]**.

RESULTS

Drug excipients compatibility study

FTIR

The asymmetric CH_2 stretching vibration for cyclohexane is at 2929.03 cm-1 and 2860.84 cm^{-1}. A broad O-H stretching was observed at 2860.84 cm^{-1} and two bands arising from C-O stretching and O-H bending appear in the spectra of carboxylic acid at 1328.67 cm^{-1} and 1472.19 cm^{-1} respectively. The band at

1615.38 cm^{-1} is due to N-H bending and at 1298.44 cm^{-1} for C N stretching vibration. The IR spectrum of ethyl cellulose is shown in **Figure 1**. It shows a broad absorption band at 2877.02 cm^{-1} due to the stretching frequency of the –C-H group of methyl/methylene. The band at 2977.36 cm^{-1} is due to C-H stretching vibration. The band around 1448.02 cm^{-1} and 1379.83 cm^{-1} are assigned to –CH2 scissoring and –O-H bending vibration respectively. The band at 1057.0 cm^{-1} is due to >CH-O-CH2 stretching and at 1749.67 cm-1 a due to strong carbonyl absorption. The band at 917.86 cm^{-1} is due to C-O-C symmetrical stretching. The Eudragit S 100 the peak contains OH (3140 cm^{-1}), CH Stretching Aromatic (3020 cm^{-1}), CH Stretching Aliphatic (2862 cm^{-1}), C=O (1630 cm^{-1}), Al-CH-bend (1334 cm^{-1}), Ar CH in plane Bending (1082 cm^{-1}). The existence of carbonyl, hydroxyl, and acetyl groups in xanthan's structure has been established. There was no evidence of a substantial interaction between the medication and the polymer in the studies.

DSC study

The interaction between drug and polymer was checked by DSC and results revealed absence of any interaction among the selected polymers and drug. The melting point of the components in the optimized formulation was not altered indicating the compatibility between drug and polymer **(Figure 2)**.

Preparation and evaluation of gastroretentive sustained release tablets using 3^2 factorial design

Initially, preliminary batches of gabapentin gastro-retentive tablets were prepared and evaluated by changing the amount of polymers Eudragit and hydroxyl ethyl cellulose. The results of the preliminary batches were used to design the factorial design batches.

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 were evaluated each at three-level and experimental trials were performed for all nine possible combinations.

Pre-compression parameters

The pre-compression parameters for the designed formulations are presented in **Table 2**. The designed formulations exhibited good flow properties as evident from the values of

Carr's index, Hausner's ratio and angle of repose.

Post-compression parameters

The designed formulations were evaluated for post-compression parameters and results displayed that all the parameters were within the acceptable limit. The friability of the tablets was less than 1% which is acceptable. Besides, the tablets exhibited sufficient hardness (5.23-5.63 Kg/cm^2) and drug content (97.62-99.87%) **(Table 3)**.

Floating Study (Buoyancy Study)

For all of the formulations, the buoyancy lag time ranged from 489 s (8.15 min) to 556 s (9.26 min). The amount of CO2 created within the tablet was related to the length of buoyancy. The FFG2 batch had the fastest buoyancy time of 556.23 s. (9.26 min).

Swelling Behavior of Tablets

The batch FFG2 containing hydoxyethyl cellulose, xanthan gum, and Eudragit exhibited highest swelling index of 103.46%. The swelling index increased with increase in polymer content. As a result, the polymer's viscosity influenced the swelling process, matrix integrity, and floating capabilities.

Dissolution Study

Dissolution study was conducted in 0.1 N HCl using USP type-II apparatus. The drug release form all the formulation was good. However, the batch FFG2 exhibited maximum drug release of 99.75%. The profile of drug release presented in **Figure 3**.

Drug Release Kinetics

The mechanism of the drug release was predicted by fitting the data to different models. The R^2 values calculated for different formulations but good correlation was observed with Korsmeyer–Peppas model (R^2=0.9983). Moreover, n value was 0.9250 indicating the non-Fickian release. Hence, the drug release followed the Korsmeyer–Peppas model.

ANOVA study and response surface analysis

ANOVA study was performed on the dependent variables drug release and floating lag time. The effect of independent variables(X1 and X2) was significant ($p < 0.05$) on the selected responses. The response surface plots give the relationship between the dependent and independent variables, or the impacts of two variables on the responses at the same time. The results of the response surface study for drug release and floating lag time were interesting. The model proved significant, with F-values of 625.96 and 124.72 for drug release and floating lag time, respectively. When the value of "P" is less than 0.0500, model terms are significant.

Stability

The stability study of optimized FFG2 formulation was conducted. The results reveled formulation was stable and no substantial change in the properties such as floating time, swelling index, and *in vitro* drug release was observed. Therefore, optimized formulation was stable at conditions of the study **(Table 4)**.

In-vivo Study

The batch FFG2 was chosen for an in vivo x-ray imaging study in rabbits to assess the tablet's stomach residence period. Photomicrographs taken at 0, 3, 6, 9, and 12 hours are shown in **Figure 4**. A pill was plainly visible in the upper small intestine, and it remained in the stomach undisturbed by drug release in rabbits. Furthermore, floating matrix tablets containing gabapentin floated in gastric fluid for 12 hours in the upper part of the rabbit's small intestine, showing great in vivo residence time, according to the research.

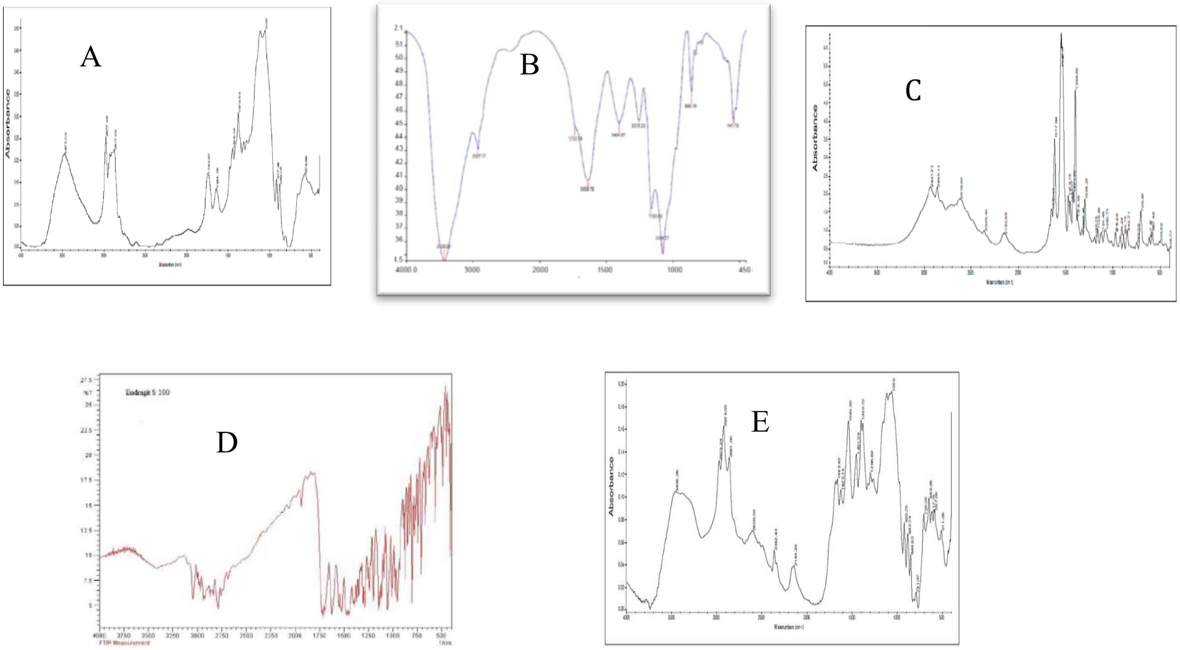
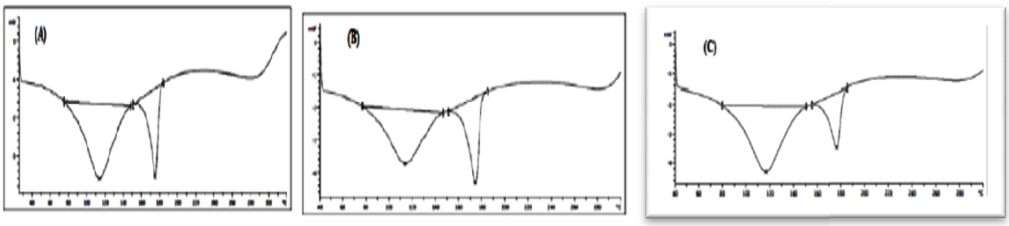


Figure 1: FTIR of A) Gabapentin B) Xanthan gum C) Hydoxyethyl cellulose D) Eudragit S-100 E) Optimized formulation



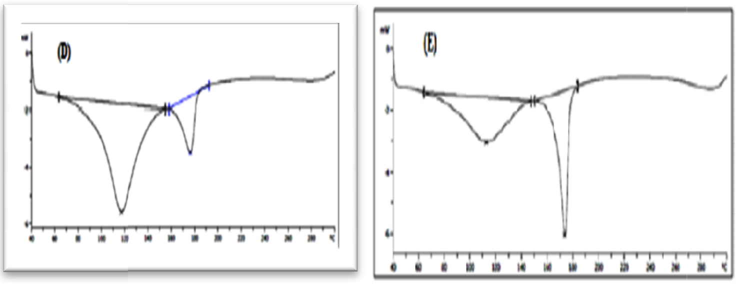


Figure 2: DSC of A) Gabapentin B) Hydroxy ethyl cellulose C) Eudragit S-100 D) Xanthan gum E) Optimized formulation

Table 2: Pre-compression parameters of designed formulations

Formulation code	Bulk density (g/cm3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's ratio	Angle of repose (θ)
FG1	0.327±0.02	0.38±0.024	13.95±0.6	1.16	24.7±1.03
FG2	0.353±0.01	0.385±0.022	8.31±0.3	1.09	23.8±1.15
FG3	0.329±0.03	0.414±0.019	20.53±0.93	1.26	23.8±1.16
FG4	0.357±0.05	0.425±0.014	16.00±1.05	1.19	24.6±1.22
FG5	0.325±0.02	0.382±0.018	14.92±0.61	1.18	21.9±1.05
FG6	0.353±0.04	0.41±0.022	13.90±1.25	1.16	24.3±1.18
FG7	0.354±0.02	0.419±0.016	15.51±1.03	1.18	25.2±1.48
FG8	0.386±0.01	0.45±0.032	14.22±0.39	1.17	26.7±1.22
FG9	0.387±0.05	0.46±0.023	15.87±0.19	1.19	23.3±1.1

Table 3:Post-compression parameters of designed formulations

Formulation code	Weight variation (gm) ±SD	Hardness (kg/cm^2)	Friability (%)	Content uniformity (%)	Floating lag time (s)	Total floating time (h)	% Swelling Index
FFG1	11.47±0.73	5.47±0.15	0.341±0.04	99.13±0.1	489 ± 2.31	>12	69.67
FFG2	11.50±0.63	5.60±0.16	0.254±0.07	99.87±0.4	556 ± 5.23	>12	103.46
FFG3	11.53±0.86	5.63±0.17	0.378±0.06	98.43±0.2	521 ± 4.63	>12	70.71
FFG4	11.39±0.54	5.40±0.18	0.367±0.08	98.65±0.5	534 ± 4.48	<12	72.96
FFG5	11.51±0.47	5.45±0.13	0.259±0.09	97.62±0.3	541 ± 3.45	<12	82.84
FFG6	11.63±0.70	5.23±0.12	0.383±0.08	98.51±0.1	519 ± 3.48	<12	100.34
FFG7	11.65±0.41	5.46±0.16	0.394±0.05	98.87±0.6	537 ± 4.21	>12	73.13
FFG8	11.50±0.57	5.57±0.3	0.367±0.02	99.61±0.9	541 ± 5.32	>12	79.20
FFG9	11.70±0.89	5.45±0.23	0.377 ±0.02	97.91±0.4	531 ± 4.27	>12	84.57

n = 3

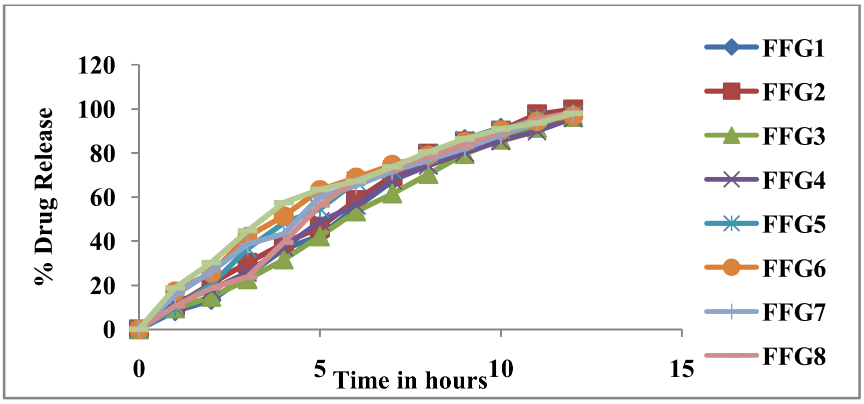


Figure 3: Drug release from the factorial batches

Table 4: Stability study of the optimized batch

Months	Floating lag time (sec)	Swelling Index (%)	In-vitro drug release (%)
1	556 ± 1.12	103.46	99.75
2	568 ± 1.32	103.55	99.60
3	578 ± 1.26	104.35	99.57
4	558 ± 1.23	103.48	99.70
5	586 ± 1.21	104.37	99.73
6	575 ± 1.35	104.49	99.71

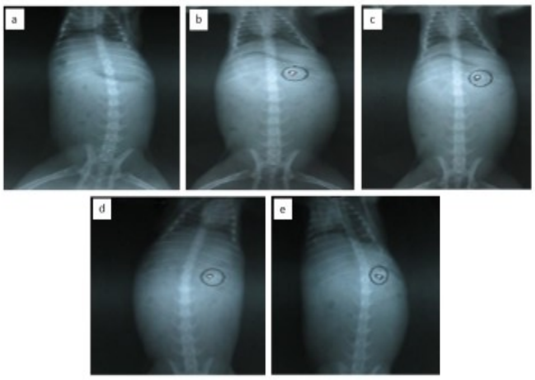


Figure 4: *In-vivo* gastric retention of gabapentin floating tablet in rabbit (a) for 0 h (b) for 3h (c) for 6 h (d) for 9 h (e) for 12 h

DISCUSSION

The present study was undertaken to develop floating gastro-retentive tablets of gabapentin for prolonging the retention of the drug in stomach. The drug-polymer interaction study was conducted using FTIR and DSC and no interaction was obtained. This was attributed to the unchanged IR absorption peaks and melting point of the drug in the presence of the polymer**. [15]** Besides, pre-compression and post-compression parameters of the designed formulations were within acceptable limits. However, batch FFG2 displayed promising evaluation properties relative to other formulations which may be due to desirable concentration of the selected polymers for the development of the tablets. **[16]** The drug release from the FFG2 formulation was maximum (99.75%) showing the optimized concentration of the selected polymers. Moreover, the floating time and swelling behavior of the batch FFG2 was more relative to other formulations. The swelling of the tablets was related to the rise in polymer content. The ANOVA study and response surface analysis indicated that the selected independent variables significantly affected the responses ($p<0.05$). Hence, the 3^2 factorial designs were valid and appropriate for the design and development of the gastroretentive tablets. Furthermore, the designed tablets were found stable as no changes in evaluated parameters were observed after the stability study. Previous investigations have come up with similar results **[17]**.

Finally, the residence time of the optimized FFG2 batch was determined in the rabbit through in vivo X-ray imaging study and tablets were floated in the stomach for 12 hrs. Other medications have also yielded similar outcomes.

CONCLUSION

The gastro-retentive tablets of the gabapentin were designed and developed by 3^2 factorial designs. The FTIR and DSC study showed absence of interaction between the drug and polymers. Besides, the developed tablets exhibited acceptable pre-compression and post-compression characteristics like flow properties, weight variation, hardness, friability, floating time, and swelling behavior. The FFG2 batch was optimized based on the evaluation parameters and subjected to *in-vivo* study in the rabbit. The *in-vivo* study revealed tablets floated in the stomach for 12 hrs. Therefore, the floating tablets of the gabapentin were successfully prepared and evaluated using 3^2 factorial designs which controlled the drug release for 12 hrs and followed Korsmeyer–Peppas model.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest among them.

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