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Original Article

# DEVELOPMENT AND EVALUATION OF GASTRIC FLOATING TABLETS OF RIBOFLAVIN USING BOX-BEHNKEN DESIGN

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**ABSTRACT**

**Objective:** To develop and evaluate gastric floating tablets of riboflavin that was thermally fused using an experimental design method.

**Methods:** Gastric floating tablets were developed using the Box-Behnken design. The effect of sintering on various tablet properties is assessed. The prepared floating tablets were tested for characteristics like usual tablet quality control tests with special emphasis on buoyancy studies and *in vitro* drug release studies.

**Results:** The drug-excipient incompatibility studies indicated no interactions between riboflavin and carnauba wax. Sintering the powder at 1200, °C partially decreased its crystallinity and improved drug release for up to 16 h. The tablets demonstrated good flow properties, acceptable hardness, low friability, and uniformity in thickness and diameter. Statistical models successfully optimized the formulation to achieve desired characteristics and practical compressibility. The optimal amounts of the variables, according to Design Expert® 12 software, were 59.19 mg of carnauba wax, 14.63% w/w of sodium bicarbonate, a sintering temperature of 74.68 °C, and a sintering exposure time of 1.99 h.

**Conclusion:** *In vitro* dissolution studies were conducted on the optimized formulation to verify the model's predictions. The experimental results closely matched the predictions. The optimized formulations showed a floating lag time of 104 seconds and a floating duration of 12.3 h. The obtained T90 was found to be 11.3 h which followed zero order kinetics with a non-Fickian diffusion mechanism.

**Keywords**: Box-behnken design, Floating tablets, *In vitro* release characteristics, Optimization, Riboflavin, Sintering


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## INTRODUCTION

The oral route of administration is important because it is convenient, easy to use, and promotes patient compliance [1]. However, when drugs are given in conventional dosage forms, there can be wide fluctuations in blood and tissue drug concentrations [2]. Controlled release systems can provide longer drug release, better utilization, continuous supply, fewer side effects, and lower doses [3]. For drugs that absorb in the stomach or upper GI tract, gastroretentive drug delivery systems are preferred. A gastroretentive controlled release system releases the drug slowly and continuously, favoring absorption in the upper GI tract [4]. This can improve the pharmacokinetics and pharmacodynamics of drugs that absorb in the upper GI tract. Among gastroretentive systems, floating drug delivery systems float on gastric fluid after some lag time or immediately, depending on the system type [5, 6].

Sintering involves bonding adjacent powder particle surfaces or compact particle surfaces by applying heat or solvents. In other words, sintering increases cross-linking between polymer particles [7, 8]. There are few reports using sintering in controlled drug delivery systems designed with drugs and polymers. The use of sintering to develop gastroretentive systems has also been found promising, though only with a few polymers [9].

Chemically, Riboflavin is d-Ribitol with the hydroxyl group at position 5 substituted by a 7,8-dimethyl-2,4-dioxo-3,4-dihydrobenzo[g]pteridin-10(2H)-yl group [10]. Riboflavin is a vitamin, enzyme cofactor, and nutrient. It is necessary for normal cell growth and function. It is found in foods like milk, eggs, meat, nuts, flour, and green vegetables. The richest natural source is yeast. It is found in free form in the retina, whey, and urine [11].

Riboflavin is used to treat deficiency caused by poor dietary intake. It is used for intestinal issues, stomach issues, infections, liver disease, alcoholism, cancer, and other conditions that cause deficiency [12]. It supports healthy eyes, skin, nerves, and red blood cells. It promotes normal cell growth and function. It is taken for slowing aging, canker sores, multiple sclerosis, Alzheimer's, burns, liver disease, blood pressure, and sickle cell anemia. Riboflavin is often used for migraine headaches and some cancers with low levels. It is taken orally for acne, muscle cramps, carpal tunnel syndrome, burning feet syndrome, and blood disorders like methemoglobinemia and red blood cell aplasia. It is also used for eye issues like cataracts, eye fatigue, and glaucoma [13]. The Box Behnken design is an experimental response surface methodology used for statistically optimizing formulations [14]. The floating tablets that were made were tested for characteristics including their solid-state properties, how buoyant they were in simulated digestive fluids, and how quickly the medication dissolved. The optimization process focused on the results for T90 (the time for 90% dissolution), floating lag time (the delay before the tablet started floating), and floating duration (how long the tablet remained afloat).

The objective of this study was to create and evaluate gastric floating tablets of riboflavin that were fused using a heat based on the Box-Behnken design.

## MATERIALS AND METHODS

### Materials

Riboflavin and carnauba wax, which were of analytical grade, were procured from Seeko labs in Vijayawada. All the other chemicals are of analytical grade quality and procured from Molychem Private Limited, Mumbai.

### Methods

#### Construction of standard calibration curve

Riboflavin stock solution was prepared in 0.1N HCl and aliquots of stock solution were taken to prepare working standard solutions of 10 to 50 µg/ml. The absorbance of the solutions is measured in a UV-Visible spectrophotometer at 444 nm [15, 16].

#### Drug excipient incompatibility studies

The way drugs and excipients can physically or chemically interact with each other may affect how the drug and dosage form perform in terms of bioavailability, efficacy, stability, and safety [17]. As a

result, FTIR studies were conducted to determine the chemical compatibility of riboflavin and the excipients used in the study. The FTIR spectroscopy technique was used to determine the interaction between the drug and polymer through observed changes like variations in peak positions or intensity along with the formation of new peaks [18]. Samples were analyzed using the potassium bromide pellet method, where the infrared spectra of the individual drug and excipient were compared to the spectra of their combinations in the formulation. The scan range was from 4000 to 400 cm-1 [19].

**Experimental design**

A total of four variables at three levels were utilized to design the optimization experiments. Two variables were related to the formulation: the ratio of drug to polymer and the weight percentage of the gas-producing agent per tablet. Two variables were related to the process: temperature and time. A Box-Behnken design was used to optimize the selected independent variables [20]. The responses or dependent variables were T90 (the time needed to release 90% of the drug), floating lag time (the time for the tablet to rise to the surface), and floating time (the duration the tablet remained floating). The independent variables and their levels are displayed in table 1. The critical values for obtaining the desired responses and the potential interaction effects of the selected independent variables on the responses were estimated using Design Expert software version 12. A total of 29 runs were obtained according to the Box-Behnken design for four independent variables at three levels, including 5 replicates of center points.

**Table 1: Independent variables and their levels used in box-behnken design**

| Code | Independent variable | Carnauba wax | | |
|---|---|---|---|---|
| | | Low | Medium | High |
| | | (-1) | (0) | (+1) |
| Formulation related | | | | |
| X1 | Drug-polymer ratio | 1:0.6 | 1:0.8 | 1:1 |
| X2 | Weight of gas-generating agent/tablet (%w/w) | 5 | 10 | 15 |
| Process related | | | | |
| X3 | Sintering temperature (°C) | 40 | 50 | 60 |
| X4 | Sintering time (hours) | 1 | 2 | 3 |

**X-ray diffraction (XRD) studies**

Both the unsintered and sintered powdered samples of riboflavin excipient mixtures are placed on a flat sample holder called a holder. The powder sample holder is mounted on the goniometer head of the XRD instrument. The X-ray tube, detector, and optics are configured appropriately. Parameters like tube voltage, tube current, scan range, step size, and scan speed are chosen based on the material and desired information. A voltage of 10-20 kV is applied. High-energy X-rays are generated when electrons collide with a metal target in the X-ray tube, usually copper. These X-rays have a wavelength similar to the spacing between atomic planes in crystals. The sample is continuously rotated as the X-ray beam hits it at different angles (θ). The diffracted X-rays are detected and the intensity is recorded at each angle [21]. The resulting XRD pattern of intensity vs 2θ angle is analyzed. Peaks correspond to constructive interference from atomic planes at specific angles and are used to determine structure and crystallinity [22].

**Formulation of Riboflavin gastric floating tablets (GFT)**

A total of 9 formulations were predicted using the two formulation independent variables: drug-polymer ratio and weight of gas generating agent per tablet (%w/w) according to the Box-Behnken design. The formulas are shown in table 2. These are coded as unsintered tablets. These unsintered tablets containing 50 mg of riboflavin were subjected to 29 runs as shown in table 3 to compare the effect of sintering on drug release properties.

**Table 2: Formulae of riboflavin unsintered GFT using carnauba wax**

| Ingredient (mg) | RC1U | RC2U | RC6U | RC7U | RC11U | RC20U | RC24U | RC25U | RC29U |
|---|---|---|---|---|---|---|---|---|---|
| Riboflavin | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Carnauba wax | 30 | 30 | 30 | 40 | 40 | 40 | 50 | 50 | 50 |
| Sodium bicarbonate | 6.5 | 13 | 20 | 7 | 14 | 21 | 8 | 15 | 23 |
| Microcrystalline cellulose | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium stearate | 2 | 2.5 | 2.5 | 2.5 | 2.5 | 3 | 3 | 3 | 3 |
| Total weight (mg) | 138.5 | 145.5 | 152.5 | 149.5 | 156.5 | 164 | 161 | 168 | 176 |

**Preparation of pre-compression of blend**

All ingredients for a batch of 300 tablets were screened through a sieve with an aperture of 425µm (sieve #40, ASTM). The drug and polymer were combined geometrically until a homogeneous blend was achieved using a polybag. The gas-producing agent was then added to the mixture and blended for another five minutes in the poly bag [5]. Finally, the lubricant was added and blended for an additional 30 min.

**Evaluation of flow properties**

The flow properties of the pre-compression blend were assessed using the angle of repose test, Carr's compressibility index test, and Hausner's ratio test [23].

**Preparation of GFT of riboflavin**

The tablets were compressed using a 10-station RIMEK Minipress tablet compression machine following the direct compression technique with 9 mm flat and round punches [22].

**Evaluation of GFTs of riboflavin**

The prepared gastric floating riboflavin tablets underwent testing for various characteristics after compression, like thickness and diameter, hardness, abrasion resistance, uniformity of weight, uniformity of drug content, *in vitro* floating behavior, and *in vitro* drug release [24].

***In vitro* drug release studies**

*In vitro* drug release studies were performed for the prepared formulations using a USP type II (paddle method) dissolution apparatus Lab India DS-8000. The dissolution medium was 900 ml of 0.1N HCl maintained at 37 °C±0.5 °C. The paddle speed was set at 50 rpm. The study was conducted for 12 h and 5 ml samples were withdrawn at fixed time intervals using a syringe fitted with a filter. 5 ml of fresh medium maintained at 37 °C±0.5 °C was used to replace the volume at each interval by washing the particles stuck to the filter back into the dissolution medium [25]. The collected samples were analyzed for riboflavin by measuring the absorbance at 444 nm using a UV-visible spectrophotometric method.

**Table 3: Preparation of riboflavin sintered GFT using carnauba wax as per the predicted runs**

| Run No. | Formulation code | X1 (mg) | X2 (mg) | X3 (°C) | X4(h) |
|---|---|---|---|---|---|
| 1 | RC1 | 30 | 6.5 | 50 | 2 |
| 2 | RC2 | 30 | 13 | 50 | 1 |
| 3 | RC3 | 30 | 13 | 50 | 3 |
| 4 | RC4 | 30 | 13 | 40 | 2 |
| 5 | RC5 | 30 | 13 | 60 | 2 |
| 6 | RC6 | 30 | 20 | 50 | 2 |
| 7 | RC7 | 40 | 7 | 40 | 2 |
| 8 | RC8 | 40 | 7 | 60 | 2 |
| 9 | RC9 | 40 | 7 | 50 | 1 |
| 10 | RC10 | 40 | 7 | 50 | 3 |
| 11 | RC11 | 40 | 14 | 40 | 1 |
| 12 | RC12 | 40 | 14 | 60 | 1 |
| 13 | RC13 | 40 | 14 | 40 | 3 |
| 14 | RC14 | 40 | 14 | 60 | 3 |
| 15 | RC15 | 40 | 14 | 50 | 2 |
| 16 | RC16 | 40 | 14 | 50 | 2 |
| 17 | RC17 | 40 | 14 | 50 | 2 |
| 18 | RC18 | 40 | 14 | 50 | 2 |
| 19 | RC19 | 40 | 14 | 50 | 2 |
| 20 | RC20 | 40 | 21 | 40 | 2 |
| 21 | RC21 | 40 | 21 | 60 | 2 |
| 22 | RC22 | 40 | 21 | 50 | 1 |
| 23 | RC23 | 40 | 21 | 50 | 3 |
| 24 | RC24 | 50 | 8 | 50 | 2 |
| 25 | RC25 | 50 | 15 | 50 | 1 |
| 26 | RC26 | 50 | 15 | 50 | 3 |
| 27 | RC27 | 50 | 15 | 40 | 2 |
| 28 | RC28 | 50 | 15 | 60 | 2 |
| 29 | RC29 | 50 | 23 | 50 | 2 |

## RESULTS

### Standard calibration curve

A calibration curve for riboflavin was constructed using different concentrations of the drug in 0.1 N HCl buffer. The concentrations ranged from 10 to 60 µg/ml absorbance readings were taken for each concentration and a linear relationship was observed between the concentration and absorbance, with a very high correlation coefficient ($r^2$) of 0.999. This indicates that riboflavin exhibited excellent linearity within this concentration range in 0.1 N HCl buffer [26]. The equation derived from the calibration curve (y = 0.016x-0.006) was later used to determine the drug content in the formulations and evaluate the percentage of drug release from the formulations during the *in vitro* dissolution studies. The calibration curve is shown in fig. 1.

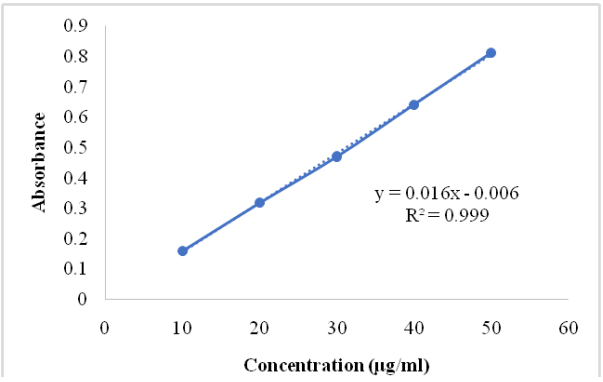


**Fig. 1: Standard calibration curve of riboflavin in 0.1N HCl**

### Drug excipient incompatibility studies

The FTIR spectra of riboflavin and carnauba wax were compared to that of their combination in the formulation to detect any chemical incompatibility. The major peaks in riboflavin spectra correspond to characteristic functional groups, including C-H, N-H, O-H, C=O, C=N, C=C, and C-C stretches. The results show that there were no major shifts in the peak positions of these functional groups in the formulation spectrum compared to riboflavin alone. All peaks were present at nearly the same wave numbers, indicating that the chemical environment and bond strengths of the functional groups remained unchanged. In addition, no new peaks appeared in the formulation spectrum that would suggest the formation of new chemical bonds or degradation products due to the interaction between riboflavin and carnauba wax [27].

These findings suggest that there is no evidence of significant chemical reaction or incompatibility between riboflavin and carnauba wax under the conditions tested. The integrity of riboflavin seems to be maintained in the formulation as the major functional groups are unaltered. However, minor shifts or changes in weaker peaks that were not detected could still point to some degree of interaction [28]. More sensitive techniques may be needed to fully rule out any incompatibility. Nevertheless, based on the FTIR results, riboflavin and carnauba wax seem to be compatible for use together in this formulation. The FTIR spectrum of riboflavin and riboflavin with carnauba wax is shown in fig. 2 and the characteristic peaks of the FTIR spectra are shown in table 4.

### X-ray diffraction studies

The XRD patterns of the powder before and after sintering are shown in fig. 1. The powder before sintering showed sharp, well-defined peaks, indicating a crystalline structure. The major peaks occurred at 2θ values of 10°, 20°, and 30°, corresponding to the (110), (200), and (211) planes of the crystal lattice. After sintering the powder at 1200 °C, the XRD pattern showed a reduction in the intensity of the peaks. Some peaks also shifted to slightly higher 2θ values. This indicates that the crystallinity of the powder decreased after sintering, likely due to partial melting and recrystallization at elevated temperatures [29]. The resultant XRD pattern is shown in fig. 3. The decrease in crystallinity of the powder after sintering has important implications for tablet properties. Crystalline materials typically have higher mechanical strength and lower solubility compared to amorphous or

semi-crystalline materials. The reduction in crystallinity and particle agglomeration caused by sintering is likely to decrease the mechanical strength of the tablets produced. This suggests that lower compaction pressures may be needed during tablet production to avoid excessive capping and lamination. The increase in amorphous content after sintering could also enhance the dissolution and solubility of any drugs incorporated into the tablets [29]. This may be beneficial if rapid drug release is desired. However, the loss in crystallinity could also make the material more hygroscopic and susceptible to instability issues over time. More studies are needed to determine the optimal sintering conditions that balance tablet properties with material stability.

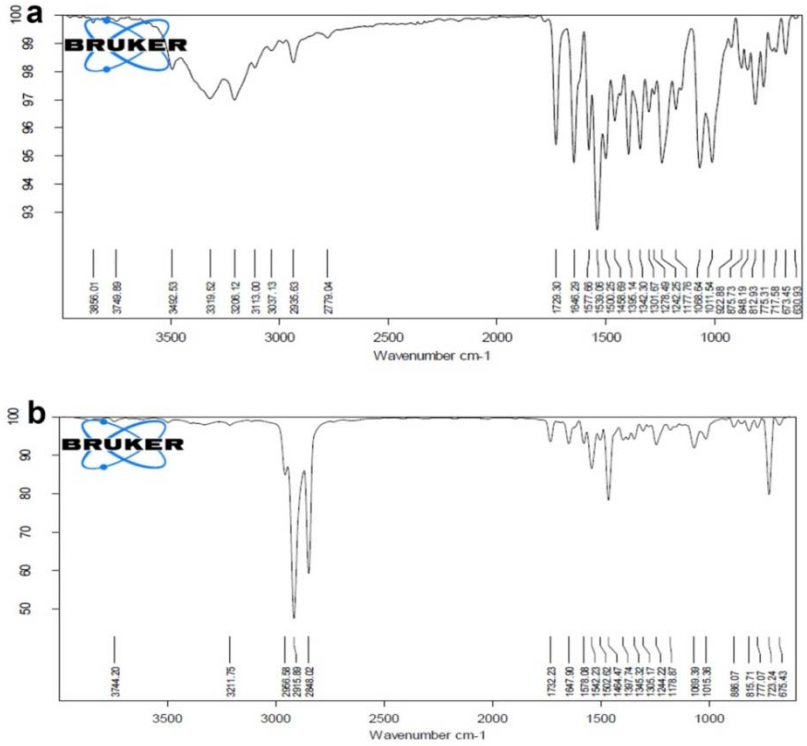


**Fig. 2: FTIR spectrum of a. Riboflavin b. Riboflavin+Carnauba wax**

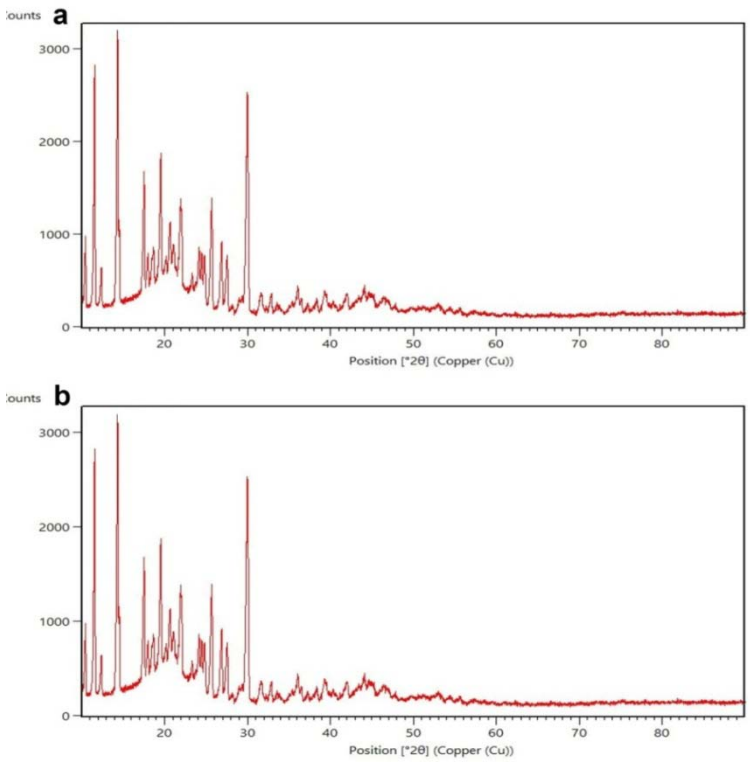


**Fig. 3: XRD patterns of a. Unsintered riboflavin powder mixture b. Sintered riboflavin powder mixture**

**Table 4: FTIR data for riboflavin and riboflavin+carnauba wax**

| S. No. | Functional group | Frequency ($cm^{-1}$) | |
|---|---|---|---|
| | | Riboflavin | Riboflavin+carnauba wax |
| 01 | C-H (stretching) | 1342.30 | 1345.32 |
| 02 | N-H (stretching) | 3319.52 | 3211.75 |
| 03 | O-H (stretching) | 3492.53 | 3744.20 |
| 04 | C=O (stretching) | 1729.30 | 1732.23 |
| 05 | C=N (stretching) | 1577.66 | 1578.08 |
| 06 | C=C (stretching) | 1539.06 | 1542.23 |
| 07 | C-C (stretching) | 1011.54 | 1015.36 |

**Flow properties**

The angle of repose of the powder blend was between 28.410 and 31.060, indicating good to excellent flow properties. The Carr's index values ranged from 11.11 to 19.69, indicating the compressibility of the powder blend, while the Hausner's ratio values were between 1.12 and 1.24, supporting the good flow of the powder blends [30]. Therefore, direct compression was used for tablet compression. Table 5 shows the results of precompression parameters.

**Table 5: Flow properties of GFT of riboflavin prepared with carnauba wax formulation powder blends**

| Formulation | Angle of repose[a] (θ) | Tapped density[a] ($g/cm^3$) | Bulk density[a] ($g/cm^3$) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| RC1U | 30.01±0.95 | 0.66±0.05 | 0.53±0.01 | 19.69 | 1.24 |
| RC2U | 29.92±0.96 | 0.65±0.01 | 0.55±0.02 | 15.38 | 1.18 |
| RC6U | 31.06±1.14 | 0.64±0.02 | 0.56±0.01 | 12.50 | 1.14 |
| RC7U | 30.12±1.07 | 0.61±0.02 | 0.52±0.03 | 14.75 | 1.17 |
| RC11U | 29.82±0.93 | 0.62±0.03 | 0.53±0.05 | 14.52 | 1.17 |
| RC20U | 29.02±0.83 | 0.63±0.05 | 0.56±0.06 | 11.11 | 1.12 |
| RC24U | 28.41±1.17 | 0.66±0.04 | 0.54±0.01 | 18.18 | 1.22 |
| RC25U | 29.86±1.02 | 0.64±0.02 | 0.55±0.02 | 14.06 | 1.16 |
| RC29U | 29.61±0.88 | 0.62±0.03 | 0.54±0.05 | 12.90 | 1.15 |

[a]Data is expressed as mean±SD, n=3

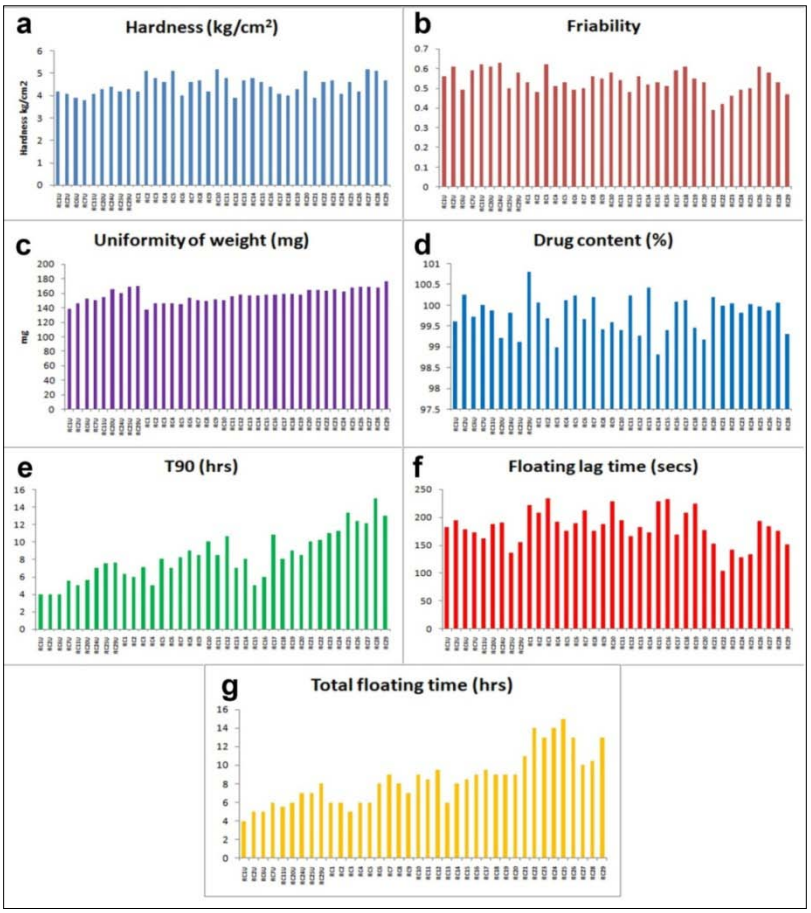


**Fig. 4: Results of post-compression parameters a. Hardness b. Friability c. Uniformity of weight d. drug content e. t90 f. Floating lag time g. Total floating time. Data is given in mean, n=3**

**Evaluation of GFTs of riboflavin prepared with carnauba wax**

The results showed that the tablets had uniform thickness and diameter. The hardness of the tablets ranged from 3.8 to 5.2 kg/cm2, ensuring good handling properties. The friability values ranged from 0.49 to 0.63%. Since this friability percentage was<1%, it indicates that the tablets are mechanically stable. All the tablets passed weight variation testing as the deviation in weight was within±7.5% of the average weight, the pharmacopoeial limit. The drug content of gastric floating riboflavin tablets prepared with carnauba wax was between 90 to 110%, indicating it meets official compendia tests for tablets [4, 7]. All formulations had floating lag times ranging from 104 to 234 seconds, while floating times ranged from 4 to 15 h. The results of post-compression parameters are shown in fig. 4.

***In vitro* drug dissolution studies**

Tablets that were not thermally fused released the drug within 5 to 9 h, while tablets that were fused extended release from 6 to 16 h with varied drug-polymer ratio, sintering temperature, and duration. The *in vitro* drug dissolution plots are shown in fig. 5. Except for RC1U, RC2U, RC6U, RC7U, RC20U, and RC13U, all formulations followed zero-order drug release kinetics. All formulations followed a diffusion mechanism based on the 'r' value. All formulations followed the non-Fickian diffusion drug release mechanism [31, 32].

**Optimization and data analysis**

The responses of the thermally fused formulations containing carnauba wax were fitted to linear, interaction, and quadratic models using Design Expert 12 software. The linear model was suggested for the T90 response and floating time, while the quadratic model was suggested for floating lag time. The models describe the effect of independent variables on responses. Various formulations within the experimental design were prepared to obtain floating tablets which were then evaluated for T90, floating lag time, and floating time.

The F values for T90, floating lag time, and floating time responses were 143.90, 597.80, and 296.42, respectively, showing significant models. The R2 values were close to 1, indicating good models. The predicted R2 values reasonably agreed with the adjusted R2 values. The adequate precision values ranged from 35.24 to 71.48, indicating the models can navigate the design space well [14].

The optimal values of variables from Design Expert® 12 software were 59.19 mg of carnauba wax, 14.63% w/w of sodium bicarbonate, 74.68 °C sintering temperature, and 1.99 h sintering exposure time (table 6).

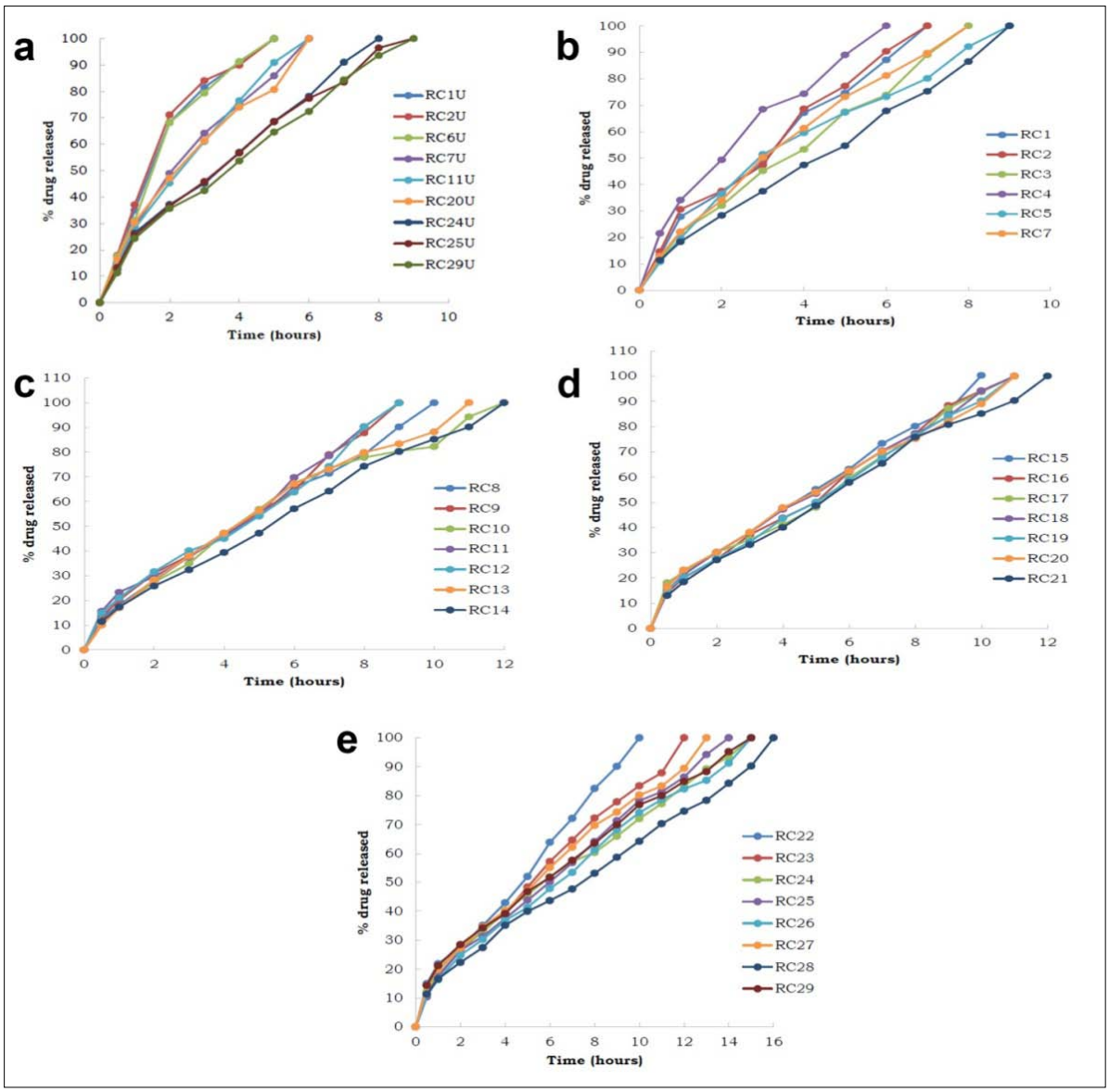


**Fig. 5: *In vitro* drug dissolution profile a. Unsintered tablets b-e sintered formulations from RC1 to RC29. Data is given in mean, n=3**

**Table 6: Formula of statistically optimized formulation, $RC_{opt}$**

| Ingredient | Quantity (mg) |
|---|---|
| Riboflavin | 50 |
| Carnauba wax | 59.19 |
| Sodium bicarbonate | 23.7 |
| Microcrystalline cellulose | 50 |
| Magnesium stearate | 3 |
| Total | 186 |

Sintering temperature: 74.68 °C; Sintering time: 1.99 h

*In vitro* dissolution studies for the optimized formulation verified the theoretical prediction. The optimized formulation showed 104 sec floating lag time and 12.3 h floating time. T90 was 11.3 h following zero-order kinetics with a non-Fickian diffusion mechanism. The % relative error between predicted and experimental response values was<5%. Desirability and overlay plots are shown in fig. 6. The comparison of predicted and observed responses of the statistically optimized formulation is shown in table 7.

**Table 7: Comparison of predicted and observed responses of statically optimized formulation, $RC_{opt}$**

| Response | Observed | Predicted | % Relative error |
|---|---|---|---|
| $T_{90}$ | 10.9 | 11.0 | 0.91% |
| Floating lag time | 104 | 100.0 | 4.00% |
| Floating time | 12.3 | 11.91 | 3.27% |

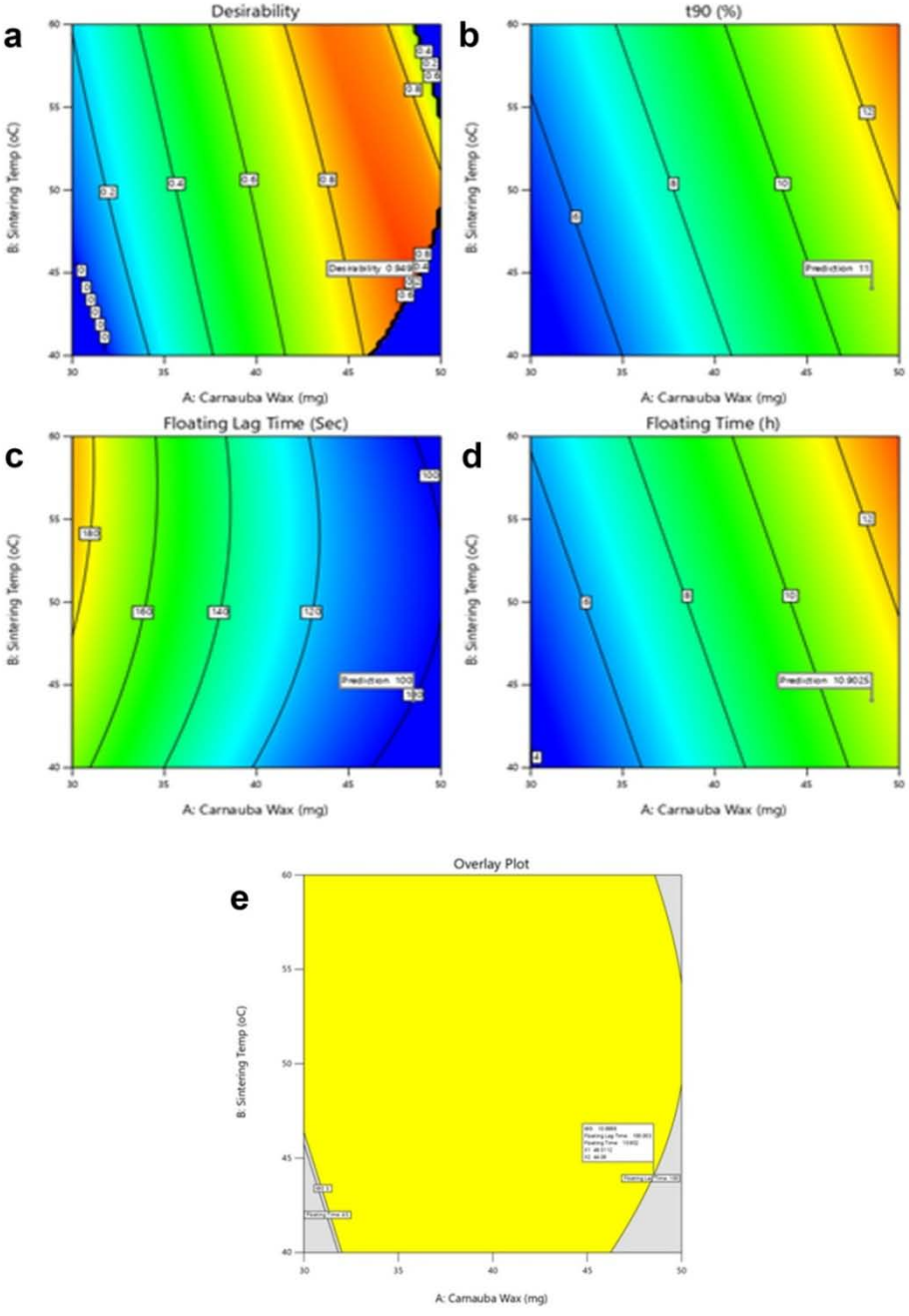


**Fig. 6: Response surface plots of a. desirability b. t90 c. floating lag time d. floating time e. overlay**

Response surface methodology (RSM) yielded regression equations relating T90, floating time, and variables in coded units (A: carnauba wax concentration, B: w/w of sodium bicarbonate, C: sintering temperature, and D: sintering time):

T90 = 9.32+3.37A+0.4583B+1.06C+0.5625D

Floating lag time = 145.33-43.88A-17.83B+7.50C+3.88D+6.50AB-4.50AC–2.75AD+0.0000BC+0.0000BD–1.0000CD–9.46$A^2$-9.86$B^2$-6.29$C^2$-9.54$D^2$

Floating time = 9.10+3.56A+0.5417B+1.12C+0.5625D

## DISCUSSION

The present study aimed to develop gastric floating tablets of riboflavin prepared with carnauba wax, which could potentially improve drug absorption and bioavailability. The results of the study showed that the developed tablets had excellent mechanical and floating properties, with controlled drug release properties. The use of the sintering technique in tablet preparation significantly affected the drug release properties of the tablets, and the drug-polymer ratio, sintering temperature, and duration could be optimized to achieve desired drug release properties for specific drug delivery applications [33, 34].

FTIR spectra indicated no incompatibilities between riboflavin and carnauba wax. Sintering the powder at 1200 °C partially decreased its crystallinity, as seen from the reduction in XRD peak intensities. This could impact tablet properties with lower compaction pressures of 3.8 to 5.2 kg/cm2 needed to avoid issues like capping and lamination during compression. The decrease in crystallinity may also enhance drug release from 11 to 16 h compared to unfused tablets that are released within 5 to 9 h. The flow properties of powder blends are crucial in ensuring that the tablets produced have consistent weight, thickness, and drug content. The angle of repose (28.4 to 31.0°) and Carr's index (11 to 19%) indicated good flow properties, enabling direct compression of tablets. The use of direct compression simplifies the tablet production process and reduces production costs, making it a desirable option for manufacturing tablets [35, 36].

The prepared gastric floating tablets showed uniform thickness and diameter, an acceptable hardness between 3.8 to 5.2 kg/cm2 for handling, low friability (<1%), and drug content of 90 to 110%. Floating lag times of 104 to 234 seconds and floating times of up to 15 h were within the desired ranges. The tablets met official compendia tests for tablets and had the potential to improve drug absorption and bioavailability [37]. The use of thermal fusion in tablet preparation significantly affected the drug release properties of the tablets, and the drug-polymer ratio, sintering temperature, and duration could be optimized to achieve desired drug release properties for specific drug delivery applications [7, 37].

The statistical models were able to describe the effects of variables on responses with significant F values (143.9 to 597.8) and high R2 values (>0.9). The optimized formulation based on the models showed 104 seconds floating lag time, 12.3 h floating time, and 11.3 h T90, within 5% of the predicted values. The results of the study suggest that the tablets prepared with the sintering technique have the potential to improve patient compliance and therapeutic outcomes when compared to unsintered tablets. The ability of the tablets to remain buoyant in the stomach for an extended period could be beneficial in maximizing drug absorption and bioavailability. The controlled drug-release properties of the tablets could also be desirable for maintaining consistent drug levels in the body over an extended period [9]. These findings have important implications for the development of effective and controlled drug delivery systems.

While the *in vitro* drug dissolution studies provide valuable information on the drug release properties of the developed tablets, further studies are needed to evaluate the *in vivo* performance of the tablets. The *in vivo* performance of the tablets could be affected by factors such as pH, food intake, and gastrointestinal motility, which could influence the floating and drug-release properties of the tablets [15, 38]. Therefore, further studies are needed to evaluate the *in vivo* performance of the developed tablets and to optimize the formulation for specific drug delivery applications.

## CONCLUSION

Based on this study, we can conclude that the Box-Behnken design was used successfully to optimize the formulation of gastric floating tablets of riboflavin using carnauba wax as the release retardant polymer and sodium bicarbonate as the gas-generating agent by applying the thermal sintering technique. The thermal sintering technique significantly improved the drug release properties, highlighting its ability to enhance the solubility and dissolution properties of the drug.

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## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICT OF INTERESTS

Declared none

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