ISSN 2063-5346

PREPARATION AND EVALUATION OF FLOATING MATRIX TABLET OF TOLBUTAMIDE AS A SUSTAINED RELEASE DRUG DELIVERY SYSTEM

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Article History: Received: 10.05.2023 Revised: 29.05.2023 Accepted: 09.06.2023

Abstract

Gastro retentive drug delivery systems stay in the stomach for a long. These are a vital option for the drugs that get dissociated into the GI tract and doesn't get solubilized in the intestinal environment owing to their alkaline pH and hence necessitate their retention in the gastric (acidic) for improvised bioavailability. Such technologies are more effective in strengthening the gastrointestinal absorption of drugs with narrow absorption windows and controlling the release of pharmaceuticals with site-specific absorption restrictions. Because of the several advantages of gastro retentive medication administration, we set out to create a gastroretentive floating matrix tablet of the antidiabetic drug Tolbutamide. Floating matrix tablets are a simple unit dosage form that benefits from releasing medication for an extended period in the stomach. Anti-diabetic drugs would have a better therapeutic impact with this dose form, allowing blood glucose levels to be managed more efficiently. The preparation and evaluation of the gastroretentive floatable matrix tablet of the antidiabetic drug Tolbutamide are explained in this study.

Keywords : Gastroretentive; Drug delivery; Tolbutamide; Antidiabetic; Floating tablets; Matrix tablet.

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DOI:10.48047/ecb/2023.12.9.97

1. Introduction

Oral medicine administration is the most prevalent administration method with a systemic effect. Oral DDS accounts for more than 80% of all dosage forms available in the market due to the high patient compliance in administration.[1] The majority of pharmaceutical professionals are presently working on developing an optimal D.D.S. that has the benefit of a single dosage for the duration of therapy and delivers the active drug straight to the chosen location. Controlled release approaches approach perfection. The predictability and repeatability of drug release, drug concentration in the target tissue, and drug therapeutic effect optimization are all part of this method, which involves controlling drug discharge in the body with a smaller and less frequent dosage.[2,3] The inability to confine the dosage form in the targeted region of the G.I.T. is one of the most challenging parts of developing a controlled release system for improved absorption and bioavailability.[4]

Medication delivery systems that are gastro retentive might linger in the stomach for a long time. Such holding devices are required for medications disintegrated in the intestine, pharmaceuticals such as antacids, antibiotics, and enzymes that are required to work locally in the gastric region of the GI tract. If the drug's solubility is less in alkaline pH, its prolonged stay in the gastric region may improve its bioavailability. Such technologies are more effective in enhancing G.I. absorption of drugs with slender absorption windows and controlling the release of pharmaceuticals with site-specific absorption restrictions. The drug delivery system's retention in the stomach prolongs total G.I. transit time, boosting bioavailability for specific drugs.[2,4] To maintain controlled stomach retention of solid dose forms, several techniques can be applied, each with benefits and cons. A unique emulsion gelation technique generates floating gel beads, ideally suited for a high water-soluble drug using sodium alginate as a polymer. This polymer is employed in the thickening and gelling of goods. It also helps create emulsions by reducing the interfacial tension between the oil and water phases. The beads float for several hours and are released in a predictable sequence.[4,5]

D-mannuronic acid and L-guluronic acid combine to form alginate, a linear copolymer. They appear as M block or G block sections entirely of one unit in alginate molecules or as a region where the monomer approximates an alternating sequence. When exposed to calcium ions or multivalent cations, sodium alginate can create stiff gels.[6,7,8] Diabetes mellitus is treated with anti-diabetic drugs that lower blood glucose levels. Except exenatide, insulin, and pramlintide, hypoglycemics, antihyperglycemic drugs are administered orally. Uses of deferent classes of anti-diabetic drugs influenced by the age of the patients and health conditions. Type 1 diabetes is an insulin-deficiency condition. Type I diabetes needs the use of insulin, which must be administered through injection or inhalation.

Diabetes type 2 is a disorder in which cells become insulin-resistant. We designed a gastroretentive floating matrix tablet of the antidiabetic pharmaceutical Tolbutamide because of the numerous advantages of gastroretentive drug administration. Floating matrix tablets are a simple unit dose form that can release in the stomach for a long time.[9] Anti-diabetic medications would have a better therapeutic effect in this dosage form, allowing blood glucose levels to be regulated more effectively. The preparation and evaluation of the gastroretentive floating matrix tablet of the antidiabetic drug Tolbutamide are described in this study.

2. Materials and Methods

2.1. Screening of the experimental parameters for making matrix tablets

Tolbutamide gastroretentive floating matrix tablets were made with the polymer hydroxyl propyl methyl cellulose (HPMC K15M), which has been shown in the literature to be an excellent release-decreasing polymer. Various floating matrix Tolbutamide tablets were manufactured to optimize the amount of HPMC K15M. It was used in the range of 10% to 30 % concentration, while other additives remained constant (tolbutamide 55%, magnesium stearate 1%, and sodium bicarbonate (NaHCO3) 15%). The characteristics of a gastroretentive floating matrix tablet were assessed using the prepared formulations. The findings obtained for the batches generated for HPMC K15M screening assisted in determining the release retarding polymer concentration in the formulation. HPMC K15 M was combined with other polymers in different concentrations to assess the drug release behaviours. Powder mixes were subjected to pre-compression and bulk properties tests as per IP. Using the direct compression technique, tablets with 500 mg of tolbutamide were made per the values shown in table 1. HPMC K15M, pullulan, poloxamer 188, sodium alginate, kappa-carrageenan, and xanthan gum were used as the drug release modifying polymers of a tablet.

2.2. Optimization of the experimental parameters for making matrix tablets

2.2.1. Experimental Design-Mixture Design

The trial-and-error method of developing a new pharmaceutical formulation takes a long time and costs much money. As a result of these issues, the pharmaceutical industry's focus has switched to various approaches to developing revolutionary drug delivery systems. Optimization methods can provide an effective and cost-effective way of forecasting the ideal composition by making a few batches. This study used a combined design to optimize the Tolbutamide gastro-retentive matrix tablet. The use of mixture design to improve several pharmacological formulations have already been studied.[16-20]

2.2.2. Simplex Centroid Design

According to early research, floating matrix tablets made with a release retarding polymer amalgamation of HPMC K15 M and κ-Carrageenan released the medicine for 8 hours and possessed the requisite floating qualities. As a result, these polymers were investigated to manufacture Tolbutamide floating matrix tablets. Based on the literature analysis and preliminary study testing, the quantities of the independent variable were identified. Mixture design, i.e., Simplex Centroid Design (SCD) was applied to optimize the formulations using sodium bicarbonate, kappa-Carrageenan, HPMC K15 M, and standalone constituents in different concentrations at three levels keeping the total concentration of the other ingredients constant. The quantities of matrix agents, *i.e.*, release hindering polymer kappa-carrageenan (X2), HPMC K4 M (X1), and gas-forming agent sodium bicarbonate (X3), were utilized as independent variables in this study (Table 2). The dependent variables were the floating lag time (Flag), drug discharged after 1 hour, and time required for 90% drug discharge. The design was implemented and analyzed using the Design-Expert® Software (version 9.0.6, Stat-Ease) in 14 trials. Table 3 shows the makeup of the batches created using this statistical methodology.

2.2.3. Validation of Model

The design expert proposed three different formulations to examine and authenticate the robustness of the prototypes established by SCD. The experimentally acquired findings of the developed formulation were matched with the mathematical prototypes. Table 4 illustrates the importance of the selected

elements utilized in the validation batch development, as calculated by the program, while maintaining all other ingredients constantly.

2.3. Method of Preparation of Tolbutamide Floating Matrix Tablets

Direct compression was used to make tablets containing 500 mg of Tolbutamide.[10] Tolbutamide, a release-decreasing polymer (HPMC K15M and pullulan/ sodium alginate/kappa-carrageenan/ xanthan gum/ carbopol 934 P/ poloxamer 188), and an effervescent-causing agent, NaHCO3, were all separately moved through sieve no. 20. Different powder mixes were blended for 10 minutes in a mortar and pestle (Table 1). The powders were then combined with microcrystalline cellulose and magnesium stearate. After another minute of mixing, the combined blend was examined for pre-compression characteristics. Finally, the required was manually balanced and served into the die of a Rotary tablet compression machine, which was furnished with a punch die capsule-shaped to manufacture caplet tablets (Dimensions – 8 mm x 17 mm with breaking).

2.4. Evaluation of Gastroretentive Floating Matrix Tablet

2.4.1. Weight Variation

Twenty pills were chosen arbitrarily and balanced precisely. The data were presented as mean values with standard deviations.

2.4.2. Drug Content

Each of the ten pills was weighed and crushed separately. In 100 mL of 0.1 N HCl, an amount of powder corresponding to the quantity of one tablet (1000 mg) was extracted. A membrane filter of 0.45 µm cellulose acetate was used to filter the fluid. After an appropriate volume make-up with 0.1 N HCl, the drug quantity was measured using a UV-Visible spectrophotometer (UV 1800 Shimadzu) at a λ_{max} of 230 nm.

2.4.3. Friability Studies

Ten tablets were arbitrarily picked from every lot and put in the container of a device for tablet friability test, as per the IP requirements (Electro quip Inst., DBK instruments). The test device's drum spun 100 revolutions in four minutes. The weight loss of the tablets throughout the rotations was used to compute the % friability of the tablets.

2.4.4. Swelling Ability

This investigation was carried out by the procedure highlighted by Dorozynski *et al.*[11] with some modifications. Weighed tablets (W1) were kept in HCl (0.1 N) and maintained at body temperature. The tablets were taken out after 8 hours and weighed again (W2), and the swell ability was measured using the following equation.

Swelling index (SI)={(W2-W1)/W1}x100

The morphological changes in the tablets were also checked before and after swelling.

2.4.5. *In vitro* Buoyancy Study

The floating behaviours of the tablets were done in a beaker. We took 200 mL (0.1 N) HCl fixed in a water bath, maintaining body temperature. The total floating duration was recorded, or the time from putting the tablet in a glass beaker containing hydrochloric acid. The floating lag time, or the time between inserting the pill inside a glass beaker containing hydrochloric acid and its buoyancy.

2.4.6. Adhesion Retention Period

The retention period was checked by studying the *in vitro* adhesion time per the procedure mentioned by Jiménez-Castellanos *et al.*[12] with modification. An agar plate (2% w/w) was made in 0.1 N hydrochloric acid (pH 1.2). With a fingertip, wet one flank of the tablet with 0.1 N hydrochloric acids and press it down into the middle of the agar plate. Afterwards, we attached these plates with the disintegration test apparatus and

operated for 5 min up and down in a 0.1 N HCl maintained at 37 ± 0.5 °C. The adhered tablets got dipped in media.

2.4.7. Drug Release Studies

In vitro drug release tests were performed in Dissolution Apparatus II, maintaining body temperature at 100 rpm. We dissolved tablets in 900 mL of 0.1 N HCl solution of pH 1.2. About 5 mL was taken from the dissolving device and filtered through a cellulose acetate (0.45 µm) membrane at various intervals. The drug was analyzed by a UV-Visible spectrophotometer at 230 nm. After sampling, 5 mL solvent was added to the dissolution media to balance the volume. The theoretical discharge of the medication was compared to the release of the generated gastroretentive formulations using a model-independent approach that calculated similarity and dissimilarity factors.[13, 14]

2.4.8. Drug Release Kinetics[15]

Among several release kinetic models, Higuchi, Korsmeyer–Peppas, zero-order, and first-order models were fitted on the release data, and the model with the highest correlation coefficient was identified.

2.4.9. Stability Studies

A storage stability study was performed as per ICH guidelines. Accelerated stability tests were performed at 40 ºC ± 2 ºC and 75 ± 5% relative humidity, and the samples were taken at the 0th, 3rd & 6th month.[21] The sampled tablets were analyzed for any statistical differences in their floatability and release behavior.

3. Results and Discussion

3.1. Preliminary Studies

Several sets of floating matrix tablets of tolbutamide were made, altering the proportion of HPMC (K15M) from 10% to 30% while maintaining the amounts of the drug, MCC, and sodium bicarbonate concentration constant. Batches made with a low HPMC K15M (10%) dissolved in 0.1N HCl, while tablets manufactured with the most excellent polymer content (30%) failed to float. HPMC K15M was shown to give good results at concentrations ranging from 15 to 25%. With a 10-second lag time, the tablets made with 15% HPMC could float for 3 hours. It was discovered that when the concentration of HPMC grew, the floating lag time and floating time also increased. As a result, it was decided to use 17% HPMC K15M for future research into the effect of combining additional polymers with HPMC on gastro retention and tablet drug release. Tolbutamide floating matrix tablets were made with the following composition (see table 1). The findings of the evaluation of these initial batches are given below.

3.2. Evaluation of Preliminary batches

3.2.1. Physical Characteristics of Floating Tablet

The physical features of the batches made in Table 1 were examined, and the findings showed that all formulations were acceptable. All sets were determined to have a hardness of 4-5.7 kg/cm^2 (Table 5). The medication content analysis revealed that the tablets produced had adequate content consistency. The drug composition was confirmed within the Indian pharmacopeia's guidelines (IP). All batches had a percentage friability of less than 1%, showing solid mechanical resistance.

3.2.2. *In vitro* Buoyancy Studies

Table 6 shows the result of the buoyancy studies. The floating time of all the batches was found to be more than 8 hours; however, floating lag time was less than 31 sec. *In vitro* buoyancy is usually affected by the viscosity of the gelling polymer.[22] That means the gel strengths changes with the increase in polymer ratio, which may affect tablet flowability ultimately.[23] The distinction of the polymers employed in conjunction with HPMC did not influence the floating

qualities of the tablets in this investigation. This means that the amount of HPMC K 15M and sodium bicarbonate in tablets affects their floating properties. The floating characteristics were identical because these two amounts were the same in all formulations.

3.2.3. Swelling Ability

As indicated in table 6, the swelling indices of all the preliminary batches ranged from 1.734 to 3.864. Batch 2 with k-carrageenan showed the highest swelling index that complies with the results presented by Dorozynski *et al.*, where HPMC and carrageenan combination showed increased swell-ability of HBS-formulations. They hypothesized that this blend is useful as a base polymer for making formulations for controlled drug release.[24] It remained stable for 8 hours and distorted after 24 hours, indicating a reasonable duration needed for the passage from the stomach after drug release. The formulation with sodium alginate had the lowest swelling index, indicating that the polymer does not increase water absorption by a polymeric matrix containing HPMC. This is due to sodium alginate's pH-dependent solubility, as proposed by Timmins et al. They demonstrated that sodium alginate hydrates result in swelling in alkaline pH and do not form the gel layer in the stomach.[25] This formulation remained intact after 24 hours, indicating that it would not deteriorate over time.

3.2.4. Tablet Adhesion Retention Period

Because agar plates include negatively charged ions, similar to mucin covering the mucosal membrane, they were employed to test the comparative adhesion retention of the produced formulations. Because carboxyl and sulfate groups are present in agar gel, they include significant negative charges. Table 6 shows that the formulations resulted in pill retention ranging from 15 to 91 minutes. When comparing adhesion retention periods for produced tablets, it was demonstrated that tablets made with kappa-carrageenan and HPMC K15M had the highest adhesion retention of 91.44 minutes. In contrast, formulations made with sodium alginate and HPMC K15M had the lowest adhesion retention length. The kappa-carrageenan formulation stayed on the agar plate for longer than other formulations. This is because carrageenans are sulfated polysaccharides with a high molecular weight. Because hydrogen bonding or ionic contact with agar has a longer adhesion duration than other polymers. Because poloxamer 188 and sodium alginate have a limited capacity to interact with agar, they have a shorter retention duration.

3.2.5. Drug Release Studies

Table 7 shows the drug release statistics for the created floating matrix tablet. The release data's similarity and dissimilarity factors were also calculated. F1, F3, and F6 batches delayed drug release from the matrix as they were prepared using HPMC-K15M & sodium alginate, HPMC K15M pullulan, and HPMC K15M, respectively. As much as 85% of drugs got released within 8 hours from these formulations. However, F4 (with xanthan gum) and F5 (with poloxamer 188) released 50% of the medication in 2 hours. F2 (with kappa-carrageenan) was the only formulation that could keep the medicine released for 8 hours. According to the findings, formulation F2 (kappa-carrageenan and HPMC K15M) exhibited the same release design as the drug's predicted release pattern. For formulation F2, the f2 and f1 values were 92% and 1%, respectively. Because research shows that including anionic polymers in HPMC matrices is advantageous for producing a pH-independent discharge contour for weakly essential medicines, these findings are attributed to kappa-carrageenan characteristics. According to the findings, incorporating polyanionic polymer kappa-Carrageenan in an HPMC matrix

containing tolbutamide resulted in the prolonged release of the medicine with appropriate buoyancy. Another xanthan gum-based formulation (F4) could not maintain drug release for more than 6 hours and had out-of-range values of f2 and f1. The literature did not support these findings. The release behavior of medicines from several natural polymers and gums was presented by Singh et al.[26]. According to the authors, adding xanthan gum to the formulation can slow the drug's discharge. On the other hand, Xanthan gum could not maintain drug release at the quantities tested in the current investigation. Furthermore, formulation F5 with poloxamer 188 had the same release pattern as F4, although the similarity factor was only 53%. Poloxamer 188's difficulty in maintaining drug release might be due to its inability to produce a cohesive gel barrier for drug release. After two hours, both F5 and F4 released half of the medication. As a result, neither of these polymers had good discharge retarding capabilities for producing matrix formulations of hydrophilic drugs at the concentrations investigated. This might be because the formulation's polymers and medication are both hydrophilic and couldn't tolerate the dissolution conditions.

The following formulation, F6, made entirely of HPMC K15M, resulted in a delayed release of the medication, with f2 as 53%. The findings were in contrast to previous studies, which stated that when weakly essential medicines were made solely using the HPMC matrix, they released a high amount of drug at a lower pH. With an f2 value of 58%, a formulation made with sodium alginate and HPMC demonstrated delayed discharge. This might be due to sodium alginate's lower hydration and the fact that it doesn't subsidize matrix degradation and hence drug discharge at an acidic pH. Although sodium alginate and kappa-carrageenan are both anionic polymers, their drug discharge patterns were discovered to be different, which might be due to differences in polymer characteristics at different temperatures and pH. The similarity ratio requirement still needs to be met with Formula F3 made with pullulan. According to the literature, Pullulan may be utilized for various coatings on the formulation. The capability of pullulan as a discharge-decreasing polymer for floating formulations was tested in this study. Still, Formulations F3, with pullulan, also displayed deferred drug discharge almost identical to Formulation F6, implying that the presence of pullulan had little influence on the discharge profile of metformin from the polymeric matrix system. Even though all combinations tested may be adjusted by modifying the number of relevant factors in the formulations, the lots comprising kappa-carrageenan polymer showed better discharge. Furthermore, this formulation's swelling index and adhesion retention were higher than all other formulations, indicating that the formulation would be retained in the stomach. As a result, a simplex centroid design was used to enhance the gastroretentive floating matrix tablet of tolbutamide employing HPMC K 15 M and k-carrageenan to release decreasing polymers.

3.2.6. Mixture Design - Simplex Centroid Design

It was chosen to use a mixture design to optimize a gastroretentive floating matrix tablet of tolbutamide based on the findings of early investigations. A simplex lattice is an equally spaced array of points on a simplex. The lattice can be stated as q, m in a polynomial equation, where q is the number of components and m is the number of proportions or the degree of the polynomial taken by every part. The quantity of design points is estimated by 2q – 1. The design also has an overall centroid with uniformly distributed proportions. After evaluation, the batches using SCD are presented in further detail and statistical analysis of the collected

results. According to the findings of pre-compression testing, the powder mixes exhibited good flow qualities in all formulations.

3.2.7. Physical Properties of Floating Tablets of Tolbutamide

Table 8 shows the physical findings of the physical examination of MH floating tablets manufactured using SCD. The weight uniformity investigation was completed on all of the produced formulations. All batches were determined to have a hardness ranging from 3.9 to 5.8. All of the sets had drug content that was within IP's guidelines. All equations had a percentage friability of fewer than 1%, showing intense mechanical confrontation. Tablets from entirely manufactured lots floated for more than 8 hours, although the formulations M-SCD 12 and M-SCD 14 sank in the middle of the floating time study, perhaps due to the concentration of HPMC K15M, the low concentration of the gas-producing agent. The duration of tablet adherence ranged between 63.38 and 120.67 minutes. The tablet retention increased as the quantity of kappa-carrageenan in the formulations rose, which was predicted since carrageenan is a high molecular weight sulfated polysaccharide with a long adhesion duration, which might be attributed to hydrogen bonding or ionic contact with the agar. Augmented sodium bicarbonate levels, on the other hand, shortened the tablet adhesion retention duration.

The swelling index was determined to be in the range of 3.51 to 2.18. It was also discovered that increasing the quantity of kappa-carrageenan enhanced the swelling index in this situation. This is due to the polymer's ability to rapidly hydrate and absorb large amounts of water, resulting in the expansion of the polymeric matrix.

3.2.8. *In-vitro* Drug Release Study

Table 9 shows the drug release statistics. For each formulation, the similarity and dissimilarity factors were determined. It was discovered that M-SCD 3, 8, and 10 formulations could maintain drug release for 8 hours, although the release pattern differed from the anticipated release pattern of the medication. However, they were not similar in the release profile (similarity factor less than 50%) due to the presence of less HPMC K15M and high k-carrageenan level, demanding a high amount of HPMC K15M in the formulation to meet the release profile. Similarity and dissimilarity factors of other batches were in range. M-SCD 7 had the highest similarity of 79% and the lowest dissimilarity factor of 3% of all the formulas. The formulation had a medium quantity of X1 (HPMC K15M) and X2 (kappa-carrageenan) elements (0 coded value) and a small amount of X3 (sodium bicarbonate) factor (-1 coded weight). Statistical analysis is used to highlight the findings better. Batches M-SCD 9, 11, 13, and 14 were duplicate batches. Hence their release profiles are not included in table 9.

3.2.9. *In-vitro* Drug Release Kinetics

The mechanics of total drug discharge from dose forms are described by model-dependent release kinetics. Table 10 shows the findings of the model-dependent drug release kinetics investigation. Higuchi, Hixson-Crowell, Korsmeyer-Peppas, Zero-order, and first-order were the model-dependent techniques investigated for drug release kinetics. For 8 hours, the release of tolbutamide from these floating matrix tablets followed the Higuchi diffusion model with an R2 value close to 1. This model is created by charting cumulative percentage drug release vs square root of time, and it may be used to simulate changing dosage forms, notably matrix drug delivery systems.

3.2.10. Statistical Analysis

Table 11 shows the values for Flag, a one-hour-released medication, and t90 for all 14 lots (M-SCD1-M-SCD14). The findings revealed that the number of subject variables is influenced by the independent factors chosen. The floating

lag time was excellent in all formulations, ranging from 5 to 46 seconds, indicating that the independent variables did not influence the floating lag time. Depending on the formulation, the percentage of drug release in one hour ranged from 29.37 to 49.75%. In 4.68 to 6.95 hours, the formulations delivered 90% of the drug. The significance ($p < 0.05$) of the proportion of mean square variation attributable to the regression coefficient, as well as the residual error, was assessed using analysis of variance (ANOVA) (Table 12). The special Cubic Mixture model was important for floating lag time, while the further two replies monitored the Special Quartic Mixture model. Flag ($R2 = 0.9624$), drug release at 1hr ($R2 = 0.9997$), and t90 ($R2 = 0.9982$) all had excellent correlation coefficients, indicating a good match (i.e., a good match between the dependent and independent variables). Lack of Fit F-values for Y1, Y2, and Y3 was around 0.0675, 0.4934, and 0.4358, respectively, indicating that Lack of Fit is insignificant. All of the replies were subjected to a thorough statistical analysis individually.

3.2.10.1. Floating Lag Time

The outcome may be stated using the Special Cubic Mixture model for model analysis. After observing the coefficient's size and its mathematical sign, polynomial equations may determine the inferences (i.e., favourable or minus). All three parameters, sodium bicarbonate (X3), kappa-carrageenan (X2), and HPMC K15M (X1), appear to have a beneficial influence on the floating lag time of the formed floating tablets of metformin. However, X1 was shown to impact the lag floating time considerably. This indicates that when the concentration of HPMC K15M increases, the formulation experiences increased floating time. The three-way interaction was more critical, implying that the right mix of the three factors is necessary to achieve the lowest floating lag time. The experimental and projected values of the floating lag time were similar, confirming the model's appropriateness. Looking at the F statistics data, it was discovered that the model probability was more than the F value, i.e., 30.93, confirming the model's importance. An F-value of this magnitude has a 0.12% probability of happening due to noise. The p-value of less than 0.0500 further demonstrated the model's significance. X1, X1X2, X2X3, and X1X2X3 are essential to model footings in this situation.

3.2.10.2. Drug released After 1 hour.

Table 12 shows the ANOVA findings for the used model on the percentage of medication discharged after 1 hour. Looking at the F statistics data, it was discovered that the model probability was more than the F value, i.e., 1942.06, confirming the model's importance. An F-value of this magnitude has a 0.01 percent probability of happening due to noise. The p-value of less than 0.0500 further demonstrated the model's significance.

X1, X2, X3, X1X2, X2X3, $X1^2X2X3$, $X1X2^2X3$, and $X1X2X3^2$ are important model terms in this situation. The anticipated and adjusted R2 values were 0.9941 and 0.9992, respectively, indicating that the dissimilarity was less than 0.2, indicating that the dependent and independent variables were in excellent agreement.

At more significant levels of kappa-carrageenan, a ternary interaction of X1X2X3 had the most synergistic impact (X2). This suggests that when X2 concentrations rise in the three-dimensional plane, the proportion of medication discharged after one-hour rises, which may be attributed to kappa carrageenan hydration and degradation. The regression coefficient for Y2 was 0.9997, indicating that the model is the most well-fit. Similarly, the observed and anticipated percentage of medication released after 1 hour were equal, demonstrating the model's applicability.

3.2.10.3. Time to Release 90% of Drug

Table 11 shows the ANOVA findings for the used model on time to discharge 90% of the medication. Looking at the F statistics data, it was discovered that the model probability was more than the F value, *i.e.*, 349.27, confirming the model's importance. An F-value of this magnitude has a 0.01% probability of happening due to noise. The p-value of less than 0.0500 further demonstrated the model's significance. X1, X2, X3, X1X2, X2X3, $X1^2X2X3$, $X1X2^2X3$, and $X1X2X3^2$ are important model terms in this situation. The anticipated and adjusted R2 values were determined to be 0.9609 and 0.9954, respectively, indicating that the dissimilarity was less than 0.2, indicating that the dependent and independent variables were in excellent agreement.

The amount of sodium bicarbonate (X3), kappa-carrageenan (X2), and HPMC K15M (X1) in the manufactured floating tablets of tolbutamide has a beneficial influence on the time to release 90% of the medication. At more significant levels of kappa-carrageenan, a ternary interaction of X1X2X3 has the most antagonistic impact (X2). This suggests that when the concentration of X2 increases in the three-dimensional plane, the time requisite for the discharge of 90% of the medication decreases, implying early drug release from the formulation due to kappa carrageenan's quick hydration and erosion properties. The regression coefficient for Y3 was 0.9997, indicating that the model is the most well-fit.

3.2.10.4. Validation of Model

The design expert proposed three different formulations for the validation of the models. The checkpoint batches were prepared and analyzed to obtain the experimental response values. It was decided to compare the observed and projected values. Table 13 shows the actual and expected response values, and it is clear that the anticipated values were close to the actual values, indicating that the model was effectively validated. A numerical optimization approach based on the desirability function and a graphical optimization strategy based on the overlay plot were used to optimize all replies with varied objectives. Constraints on dependent variable responses and independent variables were used to arrive at the optimal formulation. Minimum, 34% to 36% and 6-7 hours were selected as restrictions for the replies, floating lag time, medication released after 1 hour, and t90, respectively. The Design Expert program generated the suggested concentrations of the independent variables based on the plots with the highest attractiveness near 1.0. Other studies have found that a large amount of kappa-carrageenan enhances the formulation's swelling index and adhesion retention time, confirming the formulation's presence in the stomach even with little fluid levels by permitting swelling and mucoadhesion approach. The M-SCD 7 and M-SCD 9 formulations (with the same composition) were determined to meet the desirability requirements and hence may be called optimal formulations. Furthermore, the formulation exhibited a reasonable swelling index and adhesion retention time, which are beneficial for assuring formulation retention in the stomach.

3.2.11. Stability Studies

The physical parameters of the improved tolbutamide gastroretentive floating matrix tablet did not change significantly after three and six months of accelerated stability testing. After three and six months of stability testing, the release pattern of the improved formulation exhibited 90% similarity (f2) to the formulation (the acceptable range of f2 is 50-100%). The variance in the pattern of release was negligible. As a result, it can be stated that formulation M-SCD7 has high stability when stored for six months at 40°C and 75% RH.

4. Conclusion

Tolbutamide floating matrix tablets were made using a direct compression approach. HPMC K15M was used as a release-modifying polymer in the preliminary batches along with pullulan, xanthan gum, kappa carrageenan, sodium alginate, and poloxamer 188. The prepared formulations' swelling, floating, adhesive duration, and drug release was tested. The formulation F2 (made with kappa carrageenan and HPMC K15M) demonstrated outstanding floating qualities, prolonged adhesion times, and sustained drug release properties with a similarity factor of 92% compared to the theoretical release of the drug. The combined influence of the three variables in the formulations was investigated using a simple centroid design. The formulation M-SCD 7 with X1 175 mg, X2 75 mg, and X3 150 mg was the best, with a reasonable floating lag time and meeting the drug release desirability criterion. The formulation also had an excellent adhesion retention time of 95.29± 4.75 minutes and a decent swelling index of 3.16, ensuring that the formulation is retained in the stomach. As a result, it was determined that adjusting the polymer content of a combination of kappa-carrageenan and HPMC K 15M could provide the necessary drug release pattern. However, increasing the quantity of kappa-carrageenan in the formulation is not ideal since it obstructs controlled drug release by enhancing the hydration of the formulation and so accelerates drug discharge from the formulation.

5. Conflict of interest: None

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Figure captions

Figure 1: Structural formula of drug Tolbutamide

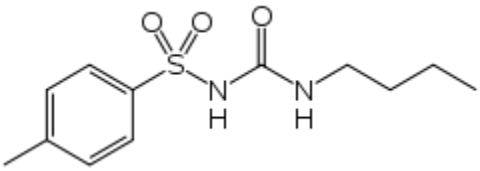

Figure 1: Structural formula of drug Tolbutamide. IUPAC Name: *N*-[(butylamino)carbonyl]-4-methylbenzenesulfonamide

Table legends

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Table 1: Composition (in percentage) of Tolbutamide Floating Matrix Tablets*

S No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Tolbutamide	55	55	55	55	55	55
2	HPMC K15M	15	15	15	15	15	15
3	Sodium bicarbonate	15	15	15	15	15	15
4	Pullulan	-	-	7	-	-	-
5	Xanthan gum	-	-	-	7	-	-
6	Sodium alginate	7	-	-	-	-	-
7	kappa-Carrageenan	-	7	-	-	-	-
8	Poloxamer 188	-	-	-	-	7	-
9	Microcrystalline cellulose	7	7	7	7	7	14
10	Magnesium stearate	1	1	1	1	1	1

*Total weight of the tablet was 1000 mg

Table 2: Aspects and their inspected values in Simplex Centroid Design for Tolbutamide

Independent Variables /Levels	Amount of HPMC K15M {X1 (mg)}	Amount of kappa-carrageenan {X2 (mg)}	Amount of sodium bicarbonate {X3 (mg)}
High	175	125	200
Low	125	75	150

Table 3: Composition of floating matrix tablets of Tolbutamide prepared by using SCD

Runs	Batch code	Transformed Fractions of Variables*			
		X1		X2	X3
1	M-SCD 1	175		50	175
2	M-SCD 2	158.33		58.33	183.33
3	M-SCD 3	150		100	150
4	M-SCD 4	150		50	200
5	M-SCD 5	183.33		58.33	158.33
6	M-SCD 6	166.67		66.67	166.67
7	M-SCD 7	175		75	150
8	M-SCD 8	158.33		83.33	158.33
9	M-SCD 9	175		75	150
10	M-SCD 10	150		75	175
11	M-SCD 11	150		100	150
12	M-SCD 12	200		50	150
13	M-SCD 13	150		50	200
14	M-SCD 14	200		50	150

*****Each tablet included 500 mg of tolbutamide, 90 mg of microcrystalline cellulose, and 10 mg of magnesium stearate in all batches. X1 denotes the quantity of HPMC K15M in milligrammes; X2 denotes the amount of kappa-carrageenan in milligrammes; and X3 denotes the quantity of sodium bicarbonate in milligrammes (mg)

Table 4: Formula for validation runs (Tolbutamide-SCD)

Factors		Composition		
		F 1	F 2	F 3
X 1	: Amount of HPMC K15M (mg)	191.82	185.14	183.33
X 2	: Amount of k-Carrageenan (mg)	56.73	64.62	66.66
X 3	: Amount of sodium bicarbonate (mg)	151.45	150.24	150.01

Table 5: Results of the physical assessment of preliminary batches of Tolbutamide floating matrix tablets

Batch code	Weight variation	Hardness (kg/cm^2)*	Drug content (%)*	Friability (%)*
F1	Complies	5.8±0.82	98.56±1.25	0.25±0.09
F2	Complies	4.2±0.62	100.94±0.94	0.23±0.12
F3	Complies	4.1±0.32	99.81±0.91	0.14±0.15
F4	Complies	4.8±0.46	102.38±0.63	0.28±0.24
F5	Complies	4.7±0.58	99.86±0.75	0.43±0.22
F6	Complies	5.2±0.85	98.75±0.88	0.12±0.28

*n=3, average of three determinations±Standard Deviation

The medication content analysis revealed that the produced tablets had adequate content consistency. The drug composition was confirmed to be within the Indian pharmacopoeia's guidelines (IP). All batches had a percentage friability of less than 1%, showing strong mechanical resistance.

Table 6 Table for values of swelling ability, buoyancy and tablet retention period for preliminary floating matrix tablets of Tolbutamide

Formulation	Lag Time*(s)	Floating Time*(h)	Tablet adhesion retention period* (min.)	Swelling index (ratio)	Physical appearance of the tablet after swelling	
					8 h (width)	24 h
F1	14.37 ± 1.16	> 9	17.36 ± 2.67	2.265	Intact 2.1 cm	intact
F2	09.95 ± 2.47	> 9	91.44 ± 4.02	4.023	2.4 cm	deformed
F3	29.88 ± 2.98	> 9	64.57 ± 4.32	3.816	2.0 cm	deformed
F4	13.32 ± 1.66	> 9	39.21 ± 3.19	3.053	2.2 cm	deformed
F5	16.43 ± 2.37	> 9	15.23 ± 3.33	2.875	deformed	deformed
F6	29.56 ± 5.11	> 9	19.68 ± 3.25	2.763	1.9 cm	deformed

*n=3, average of three readings±SD

Table 7: Results table for *in vitro* drug release and $f2$ & $f1$ values for preliminary batches of Tolbutamide matrix tablet*

Time (hrs)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	Theoretical release (%)
0	0	0	0	0	0	0	0
1	33.23±1.23	32.65±0.93	29.16±1.14	33.31±0.76	40.44±0.39	26.75±1.54	35.12±0.52
2	48.49±1.54	44.41±2.01	35.84±0.89	51.23±2.11	52.30±1.67	39.71±2.43	44.38±1.31
3	55.28±1.11	53.70±1.54	45.28±0.87	60.29±0.59	55.90±0.98	54.03±2.44	53.64±0.94
4	63.98±2.18	62.37±2.9	55.34±1.44	71.83±0.92	61.83±0.75	62.72±1.26	62.9±0.91
5	73.19±1.04	71.18±1.1	58.83±2.16	101.98±1.7	69.19±1.11	65.38±1.04	72.16±0.84
6	75.86±2.64	80.94±3.21	68.58±0.78	83.79±0.83	99.15±0.78	70.45±1.52	81.42±2.03
7	80.12±1.54	91.70±0.95	77.32±0.83	79.78±1.23	99.65±1.43	78.97±1.18	90.68±1.54
8	85.56±1.13	100.04±0.8	89.32±0.18	75.9±1.13	90.67±1.32	85.76±1.14	99.94±1.14
Similarity factor ($f2$) (%)	58	92	49	41	53	53	-
Dissimilarity factor ($f1$) (%)	7	1	15	17	10	11	-
*n=3, average of three determinations±SD							

Table 8: Physical characteristics of the tolbutamide floating matrix tablets prepared by applying SCD*

Batch code	Weight variation	Hardness (kg/cm^2)	Drug content (%)	Friability (%)	Floating Time (hrs.)	Tablet adhesion retention period (min.)	Swelling index (ratio)
M-SCD 1	Follows	3.9±0.37	99.75±0.87	0.24±0.19	> **9**	75.33±3.02	2.36
M-SCD 2	Follows	5.8±0.76	101.23±0.58	0.23±0.15	> **9**	72.48±3.98	2.32
M-SCD 3	Follows	5.8±0.56	100.08±0.63	0.28±0.11	> **9**	120.67±3.92	3.41
M-SCD 4	Follows	5.3±0.71	100.34±0.27	0.28±0.18	> **9**	71.34±2.67	2.23
M-SCD 5	Follows	5.3±0.83	100.26±0.44	0.140.22	> **9**	79.39±1.86	2.56
M-SCD 6	Follows	4.8±0.62	100.15±0.39	0.20±0.07	> **9**	90.67±1.56	2.82
M-SCD 7	Follows	4.8±0.25	101.46±0.16	0.22±0.09	> **9**	95.29± 4.75	3.16
M-SCD 8	Follows	4.9±0.84	100.18±0.19	0.24±0.12	> **9**	99.68± 2.19	2.91
M-SCD 9	Follows	4.6±0.44	101.06±0.86	0.30±0.16	> **9**	95.76±2.05	3.10
M-SCD 10	Follows	4.3±0.48	100.02±0.46	0.24±0.23	> **9**	86.47±1.28	2.98
M-SCD 11	Follows	5.3±0.73	101.36±0.75	0.31±0.17	> **9**	116.57±1.98	3.51
M-SCD 12	Follows	4.9±0.26	100.92±0.32	0.31±0.25	> **9**	84.07± 2.62	3.01
M-SCD 13	Follows	5.7±0.79	101.65±0.29	0.15±0.06	> **9**	63.38±3.36	2.18
M-SCD 14	Follows	4.6±0.76	101.67±0.17	0.32±0.22	> **9**	79.39±1.45	2.94

***n=3, average of triplicate determinations±SD**

Table 9: Results Table for *in vitro* Drug Release and $f2$ & $f1$ Values for SCD Batches of Tolbutamide Matrix Tablet*

Time	**M-SCD 1 (%)**	**M-SCD 2 (%)**	**M-SCD 3 (%)**	**M-SCD 4 (%)**	**M-SCD 5 (%)**	**M-SCD 6 (%)**	**M-SCD 7 (%)**	**M-SCD 8 (%)**	**M-SCD 10 (%)**	**M-SCD 12 (%)**	**Theoretical release (%)**
1	35.06 ±1.23	33.92 ±0.93	35.47 ±1.14	36.20 ±0.76	29.37 ±0.39	35.27 ±0.43	34.54 ±1.05	48.09 ±1.06	49.75 ±2.31	39.09 ±0.66	35.12 ±0.52
2	49.63 ±0.72	50.76 ±2.01	47.98 ±0.89	56.88 ±2.11	42.67 ±0.58	49.63 ±0.72	47.25 ±2.43	72.05 ±0.29	72.16 ±1.18	50.69 ±0.72	44.38 ±1.31
3	60.78 ±0.94	66.27 ±0.79	65.74 ±0.87	64.24 ±0.59	56.92 ±0.98	61.40 ±1.73	58.80 ±0.94	83.77 ±0.69	77.25 ±0.39	68.96 ±2.43	53.64 ±0.94
4	73.57 ±0.52	74.84 ±0.83	78.04 ±1.44	74.00 ±0.92	74.99 ±0.75	75.43 ±0.52	65.59 ±0.77	88.07 ±1.65	83.49 ±0.52	72.27 ±0.44	62.9 ±0.91
5	85.22 ±1.04	80.58 ±0.92	84.42 ±2.16	90.40 ±1.73	77.58 ±1.11	81.92 ±1.04	73.80 ±1.04	96.06 ±2.36	89.42 ±1.04	81.70 ±0.93	72.16 ±0.84
6	90.98 ±0.78	93.75 ±0.42	92.32 ±0.78	92.04 ±0.83	80.59 ±0.78	91.37 ±1.52	84.29 ±0.99	100.14±1.03	103.83±0.78	84.13 ±2.81	81.42 ±2.03
7	91.94 ±1.54	93.30 ±0.95	98.05 ±0.83	94.64 ±0.71	90.64 ±0.79	89.77 ±1.32	91.80 ±1.29	103.37±1.54	108.87±0.93	91.39 ±1.54	90.68 ±1.54
8	96.81 ±1.13	96.82 ±0.82	99.32 ±0.18	100.86±1.13	98.46 ±1.18	93.80 ±1.14	101.15±0.99	102.87±0.82	104.69±1.26	95.46 ±0.92	99.94 ±1.14
($f2$) (%)	58	56	33	52	66	58	79	36	37	57	-
($f1$) (%)	9	11	23	13	6	10	3	29	29	10	-

Formulations M-SCD 11, 13, 9 and 14 were duplicate batches of M-SCD 3, 4, 7, 12, respectively. Hence, for them *in vitro* drug discharge data is not presented in the table.

***n=3, average of triplicate determinations±SD**

Table 10: *In vitro* drug model-dependent kinetics of Tolbutamide tablets prepared by applying SCD

Batch code	Higuchi model (RH)	Korsmeyer Peppas model (RP)	Hixson Crowell model (RHC)	First order (R1)	Zero order (R0)
M 1	0.9913	0.9965	0.9923	0.9765	0.9365
M 2	0.9879	0.9938	0.9772	0.9663	0.9257
M 3	0.9917	0.9898	0.9939	0.9201	0.9282
M 4	0.9883	0.9838	0.9747	0.9284	0.9094
M 5	0.9873	0.9788	0.9651	0.8529	0.9203
M 6	0.9869	0.997	0.9904	0.9774	0.9305
M 7	0.9956	0.9962	0.9769	0.8147	0.9138
M 8	0.9483	0.9636	0.9188	0.9584	0.8112
M 9	0.9646	0.9618	0.7576	0.9144	0.8202
M 10	0.9876	0.9782	0.9541	0.9733	0.8643

Table 11: Results of dependent factors chosen for SCD design for Tolbutamide floating matrix tablets*

Runs	Batch code	Floating lag time (sec)	Drug released after 1 hr (%)	Time required for 90% (hrs)
1	M-SCD 1	10.31±1.43	35.05±1.23	5.2±0.72
2	M-SCD 2	5.88±1.19	33.92±0.93	5.76±0.22
3	M-SCD 3	5.32±1.73	35.47±1.14	5.84±0.31
4	M-SCD 4	8.54±1.32	36.20±0.76	4.99±0.42
5	M-SCD 5	15.17±1.65	29.37±0.39	6.95±0.58
6	M-SCD 6	12.43±2.11	35.27±0.43	5.91±0.27
7	M-SCD 7	15.77±1.98	34.54±1.05	6.86±0.32
8	M-SCD 8	10.43±1.92	48.09±1.06	4.68±0.53
9	M-SCD 9	12.71±1.58	34.32±1.05	6.82±0.35
10	M-SCD 10	42.49±3.17	49.75±2.31	5.03±0.46
11	M-SCD 11	10.53±1.49	34.77±1.14	5.92±0.30
12	M-SCD 12	45.66±2.43	39.09±0.66	6.89±0.63
13	M-SCD 13	5.76±1.08	36.84±0.76	5.03±0.41
14	M-SCD 14	45.91±3.12	38.79±0.66	6.76±0.63

***n=3, average of triplicate determinations±SD**

Table 12: ANOVA table for dependent variables with Simple centroid design model for tobutamide floating matrix tablets

Source	Sum of Squares	Degree of freedom	Mean Square	F Value	P-value
Floating lag time (sec) (Flag)					
Model	**2765.77**	**7**	**467.85**	**30.93**	**0.0001**
Residual	**108.19**	**8**	**16.03**		
Corrected Total	**2873.96**	**14**			
Drug released after 1 hour (%)					
Model	**388.65**	**9**	**49.05**	**1942.06**	**< 0.0001**
Residual	**0.14**	**6**	**0.028**		
Corrected Total	**388.79**	**14**			
Time to release 90% of drug (t90)					
Model	**9.05**	**9**	**1.13**	**349.27**	**< 0.0001**
Residual	**0.018**	**6**	**3.235E-003**		
Corrected Total	**9.07**	**14**			

Table 13: Predicted and actual values of the responses for validation run (Check point batches) in SCD design for Tolbutamide

Responses	F1		F2		F3	
	Predicted values	**Actual values**	**Predicted values**	**Actual values**	**Predicted values**	**Actual values**
Floating lag time (sec)	31.256	34.04	23.348	25.12	22.132	23.02
Drug released after 1 hr (%)	36.167	36.22	36.366	36.28	36.176	35.88
Time required for 90% (hrs)	7.049	7.38	7.165	7.09	7.105	7.08